ARCHIVES

OF

INTERNAL MEDICINE

EDITORIAL BOARD

JOSEPH L. MILLER, Chicago

RICHARD C. CABOT, Boston — WARFIELD T. LONGCOPE, Baltimore

GEORGE DOCK, Pasadena, Calif. — WALTER W. PALMER, New York City

W. S. THAYER, Baltimore

VOLUME 37

1926

PUBLISHERS

AMERICAN MEDICAL ASSOCIATION

CHICAGO

med.
Wahr

CONTENTS OF VOLUME 37

JANUARY, 1926. NUMBER 1 PAGE

Liver Injury in Thyrotoxicosis as Evidenced by Decreased Functional Efficiency. John B. Youmans, M.D., and Louis M. Warfield, M.D., Ann Arbor, Mich. 1

Hyperglycemia: II. Physical and Chemical Studies of Human Blood from Cases of Diabetes Mellitus. Lee Foshay, M.D., Cleveland. 18

The Peculiar Forms of Infection Caused by the Bacillus of Typhoid Fever. Anastasius Landau, M.D., and M. Fejgin, M.D., Warsaw, Poland. 32

The Effect of Heart Muscle Disease on the Electrocardiogram. Arthur W. Master, M.D., and Harold E. B. Pardee, M.D., New York. 42

A Comparison of Acute Rheumatic and Subacute Bacterial Endocarditis. B. J. Clawson, M.D., and E. T. Bell, M.D., Minneapolis. 66

Water Metabolism. Edmund Andrews, M.D., Chicago. 82

Glucose Utilization in Renal Glycosuria. James E. Paullin, M.D., Atlanta, Ga. 88

The Physiology of Synovial Fluid. F. A. Cajori, Ph.D., C. Y. Crouter, M.S., and Ralph Pemberton, M.D., Philadelphia. 92

Blood Sugar Curves in Epidemic Encephalitis. J. Kasanin, M.D., and G. P. Grabfield, M.D., Boston. 102

Intestinal Chemistry: III. Salivary Digestion in the Human Stomach and Intestines. Olaf Bergeim, Ph.D., Chicago. 110

Parallelism in the Treatment of Tuberculosis and Cardiac Disease. Horace John Howk, M.D., Mount McGregor, N. Y. 118

The Vital Capacities of One Thousand Surgical Patients. Herman J. Moersch, M.D., Rochester, Minn. 128

The Refractometric and Viscosimetric Indexes of Cerebrospinal Fluid. A. Levinson, M.D., and A. M. Serby, M.D., Chicago. 144

Book Reviews. 151

FEBRUARY, 1926. NUMBER 2

The Relation of Albuminuria to Protein Requirement in Nephritis. John P. Peters, M.D., and Harold A. Bulger, M.D., with the Assistance of Carter Lee and Celia F. Murphy, New Haven, Conn. 153

Methods and Results of Oxygen Treatment in Pneumonia. Alvan L. Barach, M.D., New York. 186

Gastric Secretion in Experimental Beriberi in the Dog. Martha Belle Farnum, Chicago. 212

The Healing of Gastric Ulcers. Burrill B. Crohn, M.D.; Samuel Weiskopf, M.D., and Paul W. Aschner, M.D., New York. 217

Acute Mercuric Chloride Poisoning. Lawrence A. Kohn, M.D., Rochester, N. Y. 225

The Inorganic Phosphorus and Calcium of the Blood in Nephritis. Herbert W. Schmitz, M.D., and Edward L. Rohdenburg, B.S., New York, and Victor C. Myers, Ph.D., Iowa City. 233

Acute Febrile Anemia: A New Disease? I. C. Brill, M.D., Portland, Ore. 244

PAGE

Changes in Respiration, in Circulation and in the Coagulation Time of Blood Produced by Sodium Citrate Injections. Minas Joannides, M.D., Chicago 248

Testing of Liver Function: 1. Detoxication by the Liver. Harry Vesell, M.D., and Carl P. Sherwin, M.D., Sc.D., New York..... 257

Paroxysmal Dyspnea as a Symptom of Syphilitic Aortitis. Chester S. Keefer, M.D., and William H. Resnik, M.D., Baltimore..... 264

Evidence of Nervous Control of Leukocytic Activity by the Involuntary Nervous System. Ernst Friederich Mueller, M.D., New York..... 268

Intradermal Salt Solution Test in Cardiac Disease in Children. Harry C. Olmsted, M.D., Seattle..... 281

Excretion of Phenolsulphonphthalein in Obstructive Jaundice, Harold A. Abramson, M.D., New York..... 291

MARCH, 1926. NUMBER 3

Experimental Renal Insufficiency: The Effects of High Protein Diet in the Presence of Low Renal Function on the Kidneys, Aorta and Liver; Changes in the Blood Pressure and Concentration of Blood Metabolites. Hilding Anderson, M.D., Duluth, Minn.

I. Controls on Normal Diet..... 297

II. Protein Diet Experiments..... 313

Hemochromatosis and Chronic Poisoning with Copper. F. B. Mallory, M.D., Boston 336

Primary Carcinoma of the Liver. Virgil S. Counseller, M.D., and Archibald H. McIndoe, M.B., Ch.B., Rochester, Minn..... 363

The Effect of Liver Damage on Cholecystography in Dogs by the Use of Sodium Tetra-Iodophenolphthalein. B. M. Fried, M.D., and L. R. Whitaker, M.D., Boston..... 388

Carbon Monoxide Poisoning: A Comparison of the Present Methods of Treatment. D. C. Walton, M.D.; W. A. Eldridge, Ph.G.; M. S. Allen, B.S., and M. G. Witherspoon, B.S., Edgewood, Md..... 398

The Enzymic Activity of the Duodenal Contents Following the Ingestion of Pancreatin. A. H. Aaron, M.D.; J. V. Wadsworth, M.D., and H. C. Schneider, M.D., Buffalo, N. Y..... 408

The Relation of Thrombocytes to Hemorrhagic Diathesis. I. W. Held, M.D., New York 414

The Value of a Starch-Iodin Reaction as a Test of Pancreatic Function. George Morris Piersol, M.D.; H. L. Bockus, M.D., and Harry Shay, M.D., Philadelphia..... 431

Some Metabolic Aspects of Calcium Therapy. A. P. Briggs, M.D., St. Louis..... 440

Effects of Intravenous Injections of Acriflavine in Sepsis. C. F. Tenney, M.D., and Joseph Lintz, M.D., New York..... 445

Book Reviews 451

APRIL, 1926. NUMBER 4

The Mechanism of Cancer Metastasis. Montrose T. Burrows, M.D., St. Louis 453

Chronic and Acute Arteritis of the Pulmonary Artery and of the Patent Ductus Arteriosus. Karl Schlaepfer, M.D., Milwaukee..... 473

The Possible Relationship Between Acromegaly and Diabetes, with Report of Three Cases. Henry J. John, M.D., Cleveland..... 489

PAGE

The Mechanism of Insulin Action. Ernst Friedrich Mueller, M.D.; Herbert J. Wiener, M.D., and Renee v.E. Wiener, Ph.D., New York.... 512

Gastric and Duodenal Ulcer: Theoretical and Clinical Studies. A. Winkelstein, M.D., New York..... 541

The Therapeutic Use of Diets Low in Water and in Mineral Content. Norman M. Keith, M.D.; Florence H. Smith, B.S., and Mary Whelan, M.A., Rochester, Minn..... 550

Water Metabolism: II. Further Observations. Edmund Andrews, M.D., Chicago 559

The Effect of Digitalis on Ventricular Premature Contractions. Harold L. Otto, M.D., and Harry Gold, M.D., New York..... 562

Pressure on the Central Nervous System in Its Relation to Hyperglycemia: Chronic Piqûre. Wiktor Z. Tychowski, M.D., and Caroline Crowell, Philadelphia 567

Book Reviews 596

MAY, 1926. NUMBER 5

Blood Pressure in Women as Influenced by the Sexual Organs. Walter C. Alvarez, M.D., and Arnold Zimmermann, Dr. és. Sc., San Francisco.. 597

Exophthalmic Goiter: A Follow-Up Study of Cases Treated with the Roentgen Ray. Bertram J. Sanger, M.D., New York..... 627

An Occupational Disease Among Zinc Workers. Carey P. McCord, M.D., and Alfred Friedlander, M.D., with the Collaboration of William E. Brown, M.D., and Dorothy K. Minster, A.B., Cincinnati..... 641

The Blood in Smallpox During a Recent Epidemic. Kano Ikeda, M.D., Minneapolis 660

Gastric Secretion in Diabetes Mellitus: Report of Ten Diabetic Patients Who had Diarrhea and Achlorhydria. Byron D. Bowen and A. H. Aaron, Buffalo 674

Hemoglobin, Color Index, Saturation Index and Volume Index Standards: Redeterminations Based on the Findings in One Hundred and Thirty-Seven Healthy Young Men. Edwin E. Osgood, M.D., Portland, Ore.. 685

Estimation of Transverse Cardiac Diameter in Man. Fred J. Hodges, M.D., and J. A. E. Eyster, M.D., Madison, Wis..... 707

The Effect of Lead and Radium on Mature and Immature Red Blood Corpuscles. Herman E. Pearse, M.D., Boston..... 715

Blood Changes in the Antepartum and the Postpartum Period of Young Mothers. Isidore Handelman, A.M.; Anton Rose, Ph.D., and Carl P. Sherwin, M.D., Sc.D., New York..... 725

JUNE, 1926. NUMBER 6

Arteriosclerosis and Increased Blood Pressure: Experimental Production. Franklin R. Nuzum, M.D.; Beatrice Seegal, M.D.; Ruth Garland, M.D., and Margaret Osborne, M.S., Santa Barbara, Calif..... 733

Diagnosis of Pulmonary Neoplasm. Maurice Fishberg, M.D., New York.. 745

The Diagnostic Aid in Evaluating the Vigor of Inspiratory Costal Excursion. C. F. Hoover, M.D., Cleveland..... 773

Corrigan's Description of Aortic Insufficiency. Edited, with a Note, by Logan Clendening, Kansas City, Mo..... 780

A Confirmatory Sign of Free Fluid in the Pleural Space: Preliminary Report. Martin Lasersohn, M.D., Richmond, Va..... 793

Biliary System Function Tests. William P. Murphy, M.D., Boston..... 797

PAGE

Water Metabolism: III. Dehydration Fevers. Edmund Andrews, M.D., Chicago 815

A Method for the Continuous Quantitative Estimation of Gastric Secretion and Discharge in Man. Arthur L. Bloomfield, M.D., and Chester S. Keefer, M.D., Baltimore 819

The Relation of the Erythrocyte Sedimentation Reaction to the Ability of Flocculation of the Plasma and Serum. E. H. Rubin, M.D., New York 848

The Seasonal Variation in the Onset of Acute Diabetes: The Age and Sex Factors in 1,000 Diabetic Patients. S. Franklin Adams, M.D., Rochester, Minn. 861

Book Reviews 865

FEB 1 1926

VOLUME 37 NUMBER 1

ARCHIVES
OF
INTERNAL MEDICINE

EDITORIAL BOARD

JOSEPH L. MILLER, Chicago

RICHARD C. CABOT, Boston WARFIELD T. LONGCOPE, Baltimore

GEORGE DOCK, Pasadena, Calif. WALTER W. PALMER, New York City

W. S. THAYER, Baltimore

JANUARY 15, 1926

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $6.00

Entered as Second-Class Matter, January 23, 1905, at the Postoffice at Chicago, Illinois, Under Act of Congress of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized on June 24, 1918.

CONTENTS OF PREVIOUS NUMBERS

NOVEMBER, 1925. NUMBER 5

Peripheral Pulsations in the Veins in Congestive Failure of the Heart, Associated with Pulsation of the Liver and Tricuspid Regurgitation. Wm. J. Kerr, M.D., and S. L. Warren, M.D., San Francisco.

Vital Capacity, Respiratory Frequency, Pulse Rate and Systolic Blood Pressure in Heart Disease: Their Importance in the Classification of Patients. Herbert W. Schmitz, M.D., New York.

Clinical Diagnosis and the Intestinal Flora. Hiromu Tsuchiya, M.D., Battle Creek, Mich.

Defects of Membranous Bones, Exophthalmos and Diabetes Insipidus: Report of a Case with Necropsy. Chester O. Thompson, M.D.; J. Jay Keegan, M.D., and A. D. Dunn, M.D., Omaha.

Lipemia and the Reticulo-Endothelial Apparatus. B. S. Oppenheimer, M.D., and Arthur M. Fishberg, M.D., New York.

Renal Injuries by Amino-Acids. L. H. Newburgh, M.D., and Phil L. Marsh, M.D., Ann Arbor, Mich.

The Effect of Changes in Position of the Heart on the Q-R-S Complex of the Electrocardiogram. Walter J. Meek, Ph.D., and Allen Wilson, A.M., Madison, Wis.

The Auricular Wave (P) of the Electrocardiogram: Clinical Observations with Especial Reference to Pulmonic and Mitral Stenoses. A. A. Alexander, M.D., Oakland, Calif.; H. F. Knight, M.D., Rochester, N. Y., and Paul D. White, M.D., Boston.

The Action of Paraphenylendiamin: An Experimental Study. Kaethe W. Dewey, M.D., Chicago.

Intermittent Auricular Fibrillation, with Fleeting Rapidly Recurring Paroxysms Having Identical Type of Auricular Behavior. Charles C. Wolferth, M.D., Philadelphia.

Roentgen-Ray Treatment of the Spleen in Asthma Bronchiale: Preliminary Report. George L. Waldbott, M.D., Detroit.

The Nonspecific Protein Reaction. Florence B. Seibert, Ph.D., Chicago.

Book Reviews.

DECEMBER, 1925. NUMBER 6

The Antigenic Property of Pollens. Harry L. Huber, M.D., and Karl K. Koessler, M.D., Chicago.

The Effect on Paramecia of Blood Serums, Especially from Patients with Carcinoma. Geneva A. Daland, S.B., Boston.

Diabetes: Electrocardiographic Studies. E. P. W. Blitzsten, M.D., and D. L. Schram, M.D., Chicago.

Nonspecific Desensitization Therapy in Allergic Asthma: The Eosinophilic Index as a Guide to Intramuscular Injection of Venom Protein, with Case Report. Ralph H. Spangler, M.D., Philadelphia.

The Nature of So-Called Sino-Auricular Block. William H. Resnik, M.D., Baltimore.

Identification of Three Types of Mononuclear Phagocytes in the Peripheral Blood. Frank A. McJunkin, M.D., St. Louis.

The Etiology of Chronic Ulcerative Colitis: Experimental Studies with Suggestions for a More Rational Form of Treatment. Jacob A. Bargen, M.D., and Arch H. Logan, M.D., Rochester, Minn.

Spindle Cell Sarcoma of the Heart. Claude S. Beck, M.D., and Harvey S. Thatcher, M.D., Cleveland.

Quinidin in the Treatment of Auricular Fibrillation, Established. Paroxysmal and Transient. F. Janney Smith, M.D., and Norman E. Clarke, M.D., Detroit, Mich.

The Value of the Icterus Index in Differentiating Anemia. A. V. St. George, M.D., and A. Lincoln Brown, M.D., New York.

The Concentration of the Blood and of the Urine in Diabetic Toxemia. Harold A. Bulger, M.D., and John P. Peters, M.D., with the Assistance of Carter Lee and Celia F. Murphy, New Haven, Conn.

The Diameter of the Red Blood Cells in the Differentiation of Anemias. L. C. Grosh, M.D., and J. L. Stifel, M.D., Toledo, Ohio.

Renal Function in Persons Having Only One Kidney. Nellis B. Foster, M.D., New York.

Hyperglycemia: 1. The Relative Blood Volumes in Diabetes Mellitus. Lee Foshay, M.D., Cleveland.

Book Reviews.

Copyright, 1926, by the American Medical Association

Archives of Internal Medicine

VOLUME 37 JANUARY, 1926 NUMBER 1

LIVER INJURY IN THYROTOXICOSIS AS EVIDENCED BY DECREASED FUNCTIONAL EFFICIENCY*

JOHN B. YOUMANS, M.D.

AND

LOUIS M. WARFIELD, M.D.

ANN ARBOR, MICH.

It has long been known that injury to the liver may occur in severe cases of thyrotoxicosis and the appearance of jaundice has been looked on as a grave prognostic sign; but that liver injury is present with any considerable frequency or that it plays any important consistent rôle in the disease has scarcely been considered. It has been suggested,[1] however, that the decreased glucose tolerance occurring in cases of thyrotoxicosis, a phenomenon not as yet adequately explained, might be the result of damage to the liver.

With this possibility in mind we have made a combined study of the functional efficiency of the liver and of the glucose tolerance in cases of thyrotoxicosis[2] to determine whether damage to the liver occurs with any important frequency in this disease and whether it bears any relation to the glucose tolerance. Results of this study show that injury to the liver occurs in a surprisingly large number of instances but fail to show any constant or causal relation between the liver damage and the decreased glucose tolerance.

METHOD

The material studied consisted of a fairly consecutive series of forty-eight patients admitted to the medical service with a diagnosis of thyrotoxicosis. The patients were studied in the manner usual in such cases, and in addition tests of liver function and of the glucose tolerance were made in twenty-seven instances. In the remaining

* From the department of internal medicine, University of Michigan Medical School.

1. Sanger, B. J., and Hun, E. J.: The Glucose Mobilization Rate in Hyperthyroidism, Arch. Int. Med. **30**:397 (Sept.) 1922.

2. The word thyrotoxicosis is used in this paper to mean diseases of the thyroid gland, neoplasm excepted, characteristically associated with an increased basal metabolism. It includes the conditions variously known as exophthalmic goiter, hyperthyroidism, toxic adenoma and adenoma with hyperthyroidism.

E M
3-14-27

twenty-one the liver function was tested but the glucose tolerance was not determined. When both the liver function and the glucose tolerance were tested both tests were performed at as nearly the same time as possible, usually within a week of each other. In two cases the tests were done four weeks and in one case two weeks apart. An attempt was made to test these functions during the more severe stages of the disease, usually soon after admission, in order to avoid negative findings due to improvement under treatment. In view of the well known cardiac complications of the disease and the possibility of a disturbed liver function due to cardiac failure, patients presenting signs of any considerable heart failure were not, as a rule, used in this study. In one or two instances such patients were studied and the test of liver function deferred until compensation had been clearly established. Patients presenting complications likely to influence liver function were not used.

The functional efficiency of the liver was determined by means of the phenoltetrachlorphthalein test as modified by Rosenthal [3] and in a few instances by the levulose tolerance test, the hemoclastic crisis test of Widal, Abrami and Iancovesco,[4] and by the determination of the concentration of the bilirubin in the blood serum.

The Rosenthal modification of the phenoltetrachlorphthalein test was adopted as the standard test of liver function. Five milligrams of the dye per kilogram of body weight, well diluted with warm physiologic sodium chlorid solution, were injected intravenously by the use of a three-way stop-cock and syringe apparatus or with simply a 50 c.c. Luer syringe. Blood was subsequently withdrawn from the opposite arm for examination. In the earlier cases samples of blood for the determination of the dye concentration were withdrawn at fifteen minute and one hour intervals after injection, as in the original Rosenthal technic. Later the hour specimen alone was drawn. While the fifteen minute specimen is useful, it was felt that the hour specimen gave the essential information and that the additional information gained by the use of the fifteen minute specimen did not justify the extra venipuncture in these cases.

The determination of the percentage of the dye in the blood serum was first done by the original Rosenthal technic; later the modifications of Bogen,[5] Blum and Rosenau [6] and the later modification of Rosen-

3. Rosenthal, S. M.: A New Method of Testing Liver Function with Phenoltetrachlorphthalein, J. A. M. A. **79**:2151 (Dec. 23) 1922.

4. Widal, F.; Abrami, P., and Iancovesco, V.: Digestion Hemoclasis Test in the Study of Hepatic Insufficiency, Presse méd. **28**:893, 1920.

5. Bogen, E.: A Clinical Test for Liver Function, J. Clin. & Lab. Med. **8**:619 (June) 1923.

6. Blum, W., and Rosenau, W. H.: The Reaction of the Liver to Phenoltetrachlorphthalein in Early Obstructive Jaundice, Arch. Int. Med. **34**:446 (Oct.) 1924.

thal,[7] similar to that of Bogen, were used. While in an occasional case none of these methods are entirely satisfactory the later method of Rosenthal was found to be the most generally useful. The acetone method of Blum and Rosenow has, in our hands, frequently failed completely to remove all the coloring matter from the serum. The exact cause of this failure has not been determined and may not be inherent in the method itself.

A retention of 3 per cent. or more of the dye in the blood serum at the end of one hour has been considered evidence of an impairment of liver function. While this figure may seem rather low, we believe it is justified by the practically entire absence of retained dye in the serum of a number of normal controls and a large number of patients with miscellaneous diseases who have given a normal response to the test.

A word regarding reactions seems advisable. A general reaction occurred five times, or in 12.5 per cent. of the patients; in this series and in a total of some ninety tests by this method general reactions have occurred only seven times. The typical general reaction is characterized by a more or less severe chill, coming on with considerable regularity about one hour after the injection of the dye, and followed by a moderately high fever. The patient complains of general body pain and malaise. Occasionally the fever or the chill is lacking. Nausea and vomiting were not noted and diarrhea occurred in only a single case. Not infrequently the patient noticed a feeling of increased well-being after the reaction. Thrombosis of the vein at the site of injection occurred but once in all the times the test has been performed.

The levulose tolerance test of liver function was performed as follows: A sample of blood was obtained following a twelve hour fast and the amount of blood sugar determined. Fifty grams of levulose dissolved in two glasses of lemonade was then given by mouth and samples of blood obtained at fifteen minute, one hour and two hour intervals and their sugar content determined. The same amount (50 gm.) of levulose was given in every case since the relation of the amount of levulose to the weight seems, within ordinary limits, to be unimportant.[8] Failure of the blood sugar concentration to rise above 0.135 per cent. and the return of the blood sugar concentration to a normal or near normal figure at the end of two hours was considered to be a normal response.[8] The cost of the levulose constitutes a considerable bar to the frequent use of the test.

---

7. Rosenthal, S. M.: The Phenoltetrachlorphthalein Test for Hepatic Function; Recent Studies with the Author's Method, J. A. M. A. **83**:1049 (Oct. 4) 1924.

8. Tallerman, K. H.: Levulose Test for Liver Efficiency; Investigation of Hepatic Condition in Pregnancy, Quart. J. Med. **17**:37 (Oct.) 1923.

Widal's hemoclastic crisis test of liver function was performed as follows: The patient was fasted twelve hours and a leukocyte count was made. The patient was then given a glass of milk and a leukocyte count was made at thirty minute intervals for two hours. A drop in the leukocyte count below the fasting level was considered evidence of a disturbance in liver function. Widal and Abrami [9] have recently stated that this method of performing the test differs from the technic described by them and Iancovesco and will lead to incorrect conclusions.

The bilirubin content of the blood serum was determined according to the method described by Stettin [10] and by Bernheim; [11] in this procedure a Duboscq colorimeter with special small cups was used instead of a Bock-Benedict. An icterus index of 6, as given by Bernheim, was considered the upper limit of normal.

The glucose tolerance test was performed in the following manner: A sample of blood was obtained after a twelve hour fast and 1.75 gm. of glucose per kilogram of body weight in two glasses of lemonade was then given by mouth. Samples of blood were drawn at fifteen minute, one hour and two hour intervals after the administration of the glucose and their sugar content was determined. Failure of the blood sugar level to rise above 0.2 per cent., the occurrence of the maximum concentration by the end of one hour and the return of the blood sugar concentration to the normal or nearly normal fasting level (0.12 per cent. or less) within two hours was considered a normal response. All blood sugar determinations were done by the method of Folin and Wu.[12]

Certain features of this method of testing the glucose tolerance demand comment. The oral administration of the glucose has been criticized because of the variations in absorption of the glucose from the alimentary tract. Various procedures have been suggested to avoid this possible source of error, particularly the use of the intravenous method of administering the glucose. We decided against the use of this procedure for the following reasons: First, since our studies were particularly concerned with the liver it seemed advisable that the blood sugar concentrations be determined following normal absorption of the glucose from the intestine and transport through the portal circulation

9. Widal, F., and Abrami, P.: The Digestion Hemoclasis Test in the Study of Hepatic Insufficiency, J. A. M. A. **84**:1002 (March 28) 1925.

10. Stettin, D.: Surgical Value of Estimation of Bile Pigmentation (Icterus Index) of Blood Serum, Ann. Surg. **76**:191 (Aug.) 1922.

11. Bernheim, A. R.: The Icterus Index (a Quantitative Estimation of Bilirubinemia): An Aid in Diagnosis and Prognosis, J. A. M. A. **84**:291 (Jan. 26) 1924.

12. Folin, Otto: Laboratory Manual of Biological Chemistry, Ed. 3, New York, D. Appleton & Co., 1922.

to the liver. Second, there is evidence [13] that the amount and rate of glucose absorbed, within rather wide limits, affects the curve of blood sugar concentration but little. The changes in blood sugar concentration following glucose ingestion are not solely and directly dependent on the character of the glucose absorption. We have had some evidence of the truth of this assertion in certain patients who vomited a part of their glucose and still showed markedly abnormal curves. It is, of course, recognized that the vomiting of any considerable amount might very well affect the result, especially in cases with only a slight decrease of tolerance. If the foregoing be true, however, there is little error introduced by the failure of complete absorption of the glucose. Third, it has been shown that ordinarily the absorption of glucose from the intestine is a fairly constant and consistent process.[14] It would seem that in thyrotoxic states, in which the alimentation is characteristically good in the absence of diarrhea, absorption would be particularly rapid and complete. In order to avoid as far as possible errors due to disturbances in absorption, care was taken not to test the glucose tolerance during a period of gastro-intestinal upset, particularly during an attack of diarrhea.

The time periods at which samples of blood were taken are probably not the best for obtaining the most accurate information regarding abnormalities in the curve of blood sugar concentration. Samples taken at thirty minute, one hour and two hour intervals after the injection of the glucose would probably give a more exact picture of the process. The procedure used was adopted to permit comparison with work previously done by others.[1]

The determination of the basal metabolic rates of the patients in this series was done with the Roth modification of the Benedict portable metabolism apparatus and the usual standard technic. The graphic method was used in some of the later cases. Basal metabolic rates are expressed as percentage of deviation from normal (tables of Aub and Dubois).

RESULTS

Table 1 presents a summary of the data obtained. Of the forty-eight patients studied two failed to show definite evidence of thyrotoxicosis and in two cases the test of liver function was unsatisfactory. These four cases have been eliminated from the series and from Table 1, leaving forty-four cases for consideration.

---

13. Maclean, H., and de Wesselow, O. L. V.: The Estimation of Sugar Tolerance, Quart. J. Med. **14**:103 (Jan.) 1921. Foster, G. L.: Studies on Carbohydrate Metabolism, II, An Interpretation of the Blood Sugar Phenomena Following the Ingestion of Glucose, J. Biol. Chem. **55**:303 (Feb.) 1923.

14. Janney, N. W., and Isaacson, V. I.: A Blood Sugar Tolerance Test, J. A. M. A. **70**:1131 (April 20) 1918.

TABLE 1.—*Summary of Data*

Case	Age	Sex*	Diagnosis	Loss of Weight (Kg.)	Basal Metabolic Rate, per Cent.,† Maximum	Basal Metabolic Rate, per Cent.,† Minimum	Glucose Tolerance Index‡	Liver Function,§ Retained Dye, per Cent., 15 Minutes	Liver Function,§ Retained Dye, per Cent., 60 Minutes	Remarks
1	42	♂	Exophthalmic goiter	4.5	56.0	12.5	26.5	10	5	
2	55	♀	Exophthalmic goiter	9.0	36.0	....	20.4	8	5	Erysipelas; necropsy
3	32	♀	Hyperthyroid	3.6	21.0	17.5	17.4	4	2	Rubella
4	16	♀	Exophthalmic goiter	11.8	73.0	....	16.4	12	10	Jaundice; pneumonia; died
5	32	♀	Toxic adenoma	11.3	50.5	23.0	10.3	4	0	Mastoiditis
6	38	♀	Exophthalmic goiter	....	70.0	37.5	12.8	8	8	Jaundice; died
7	64	♂	Exophthalmic goiter	27.2	16.5	12.0	13.8	8	2	
8	20	♀	Hyperthyroid	10.0	24.6	16.5	16.6	6	0	
9	40	♀	Exophthalmic goiter	....	35.5	....	18.7	4	0	Liver palpable
10	46	♂	Exophthalmic goiter	31.8	39.5	14.0	14.5	10	5	Jaundice; auricular fibrillation; diarrhea
11	54	♀	Toxic adenoma	13.6	49.5	....	....	7	23 (R)	Auricular fibrillation; Wassermann reaction 4+
12	60	♂	Exophthalmic goiter	15.0	82.0	....	14.0	12	..	
13	37	♀	Toxic adenoma	4.5	64.0	38.5	20.2	7	4	Vomited part of glucose
14	44	♀	Exophthalmic goiter	11.3	78.0	36.0	10.4	4	0	Liver palpable
15	58	♀	Exophthalmic goiter	6.8	60.0	36.0	....	3	0	Auricular fibrillation
16	41	♀	Exophthalmic goiter	13.1	23.0	13.5	6.6	4	0	
17	36	♂	Exophthalmic goiter	11.8	105.5	37.2	16.3	4	2.5	Auricular fibrillation
18	60	♀	Toxic adenoma	7.7	50.5	9.8	13.2	7	0	
19	42	♀	Toxic adenoma	9.0	26.5	....	....	6	0 (R)	
20	19	♀	Exophthalmic goiter	18.1	66.0	34.5	9.6	5	0	
21	33	♀	Exophthalmic goiter	12.7	75.0	52.0	13.8	6	2.5	
22	30	♀	Exophthalmic goiter	5.0	68.0	61.5	....	6	1	
23	48	♀	Exophthalmic goiter	8.1	70.0	17.5	8.9	8	4	Myxodema; diphtheria
24	49	♀	Toxic adenoma	13.6	92.0	62.0	9.9	..	2	
25	49	♂	Exophthalmic goiter	13.6	61.0	40.5	14.9	..	3+	Diarrhea
26	50	♂	Exophthalmic goiter	11.8	77.5	47.0	12.8	..	4	Auricular fibrillation
27	32	♂	Exophthalmic goiter	11.8	38.0	8.0	33.5	..	0	Glycosuria
28	43	♀	Exophthalmic goiter	4.5	29.0	20.5	8.5	8	4	
29	25	♀	Toxic adenoma	9.0	21.0	....	15.6	9	3+	
30	45	♂	Exophthalmic goiter	18.1	70.0	....	Unsatis.	10	10	Vomited glucose; jaundice; necropsy
31	38	♀	Exophthalmic goiter	14.5	108.0	51.0	12.0	3	0 (R)	
32	42	♂	Exophthalmic goiter	38.6	50.0	39.5	....	2	0	Cystitis
33	44	♀	Toxic adenoma	20.0	63.5	8.0	....	..	4	Jaundice
34	19	♀	Exophthalmic goiter	9.0	78.0	31.0	....	..	1	
35	36	♀	Toxic adenoma	4.0	54.0	19.5	....	..	5	
36	51	♂	Toxic adenoma	....	16.0	9.5	....	..	3	Auricular fibrillation
37	54	♂	Toxic adenoma	....	25.0	9.2	....	..	3+(R)	Auricular fibrillation
38	49	♀	Exophthalmic goiter	7.2	73.5	34.8	....	..	5	Jaundice; auricular fibrillation
39	53	♀	Toxic adenoma	7.2	44.0	34.0	....	..	5	
40	38	♀	Toxic adenoma	34.0	93.0	28.0	....	..	10	Jaundice
41	45	♀	Toxic adenoma	2.7	45.7	....	7.1	..	5—	
42	34	♂	Exophthalmic goiter	4.5	50.0	13.6	....	..	5	Liver palpable
43	32	♂	Exophthalmic goiter	10.0	91.0	21.5	....	..	3—	
44	18	♀	Exophthalmic goiter	23.6	86.5	34.5	....	..	3—	

* In this table ♂ indicates male, ♀ female.
† Expressed as percentage of deviation from normal, tables of Aub and Dubois.
‡ Description of method by which index is obtained is given in text. Ten or below is considered normal.
§ Phenoltetrachlorphthalein method. R indicates reaction.

An examination of the results shows that of the forty-four patients twenty-two showed evidence of liver injury according to the standard test of liver function (phenoltetrachlorphthalein) used. In these twenty-two patients the percentage of dye retained in the blood serum at one hour varied from 3 to 10 per cent. In one other patient the result was doubtful. In addition to the findings with the phenoltetrachlorphthalein test the levulose tolerance test gave evidence of damage to the liver in three of the seven cases in which it was tried, the Widal test in three out of eight cases, and the bilirubin content of the blood serum was found increased in seven of the nine cases in which a satisfactory estimation of its concentration was obtained.

Strictly speaking, in nearly all the cases tested the glucose tolerance was more or less abnormal in respect to one or the other characteristic features of the curve of sugar concentration of the blood, namely, the height of the rise, the time of maximum concentration or the time of return to a normal concentration. To aid in the analysis of the results we have expressed this abnormality numerically by measuring the area subtended by the blood sugar curves in a manner described below. The figure so obtained we have called the glucose tolerance index. According to this arbitrary method, which agrees quite closely with the ordinary method of interpreting blood sugar curves in glucose tolerance determinations, the cases in this series with a glucose tolerance index figure of 20 or over are considered markedly abnormal; those with an index of from 14 to 20, moderately abnormal; those with an index of 10 or over, slightly abnormal; and those below 10, normal. So classified, four patients had a marked, nine a moderate and eight a slight decrease in glucose tolerance. Six of the patients had a normal glucose tolerance. In this normal group are placed two patients whose classification is doubtful. One (Case 20) seemed to have a slightly abnormal curve but according to the method of classification used is classified as normal. The other (Case 16) lacked the one hour blood sample. The determination of the glucose tolerance was unsatisfactory in one instance (Case 30).

Six of the patients in this series died, Patients 2, 4, 6, 24, 27 and 30. In five cases, including one patient who died after operation, Patient 24, death was apparently due directly or indirectly to the thyroid disease. One patient (Case 2) died during an attack of erysipelas. Four of the patients who died were among those in this series who gave evidence of liver injury. Three of these had been jaundiced. Necropsy was performed in two instances (Cases 24 and 30) and in both the patients had presented evidence of liver damage. One (Case 30) showed evidence of a mild chronic cholecystitis and a chronic passive congestion of the liver. The liver was of about normal size, the capsule thin and smooth. On section marked chronic passive

congestion and some fatty changes were seen. The cut section was yellowish, reddish and brown. The lobules appeared normal in size. The gallbladder was thin walled and adherent to the colon at the hepatic flexure. No gallstones were found.

In the other (Case 2) the liver was about normal in size and brown. The lobules were easily seen on the surface and more easily seen on section. The liver was congested and of the nutmeg variety.

In both cases the pathologic diagnosis of the thyroid condition was exophthalmic goiter.

ANALYSIS OF RESULTS

Analysis of the twenty-eight cases in which tests of both liver function and the glucose tolerance were done fails to show any clear relation between the presence and degree of liver damage and the glucose tolerance. Ten cases showed a decreased glucose tolerance and evidence of liver injury. Ten had a decreased glucose tolerance but gave no evidence of damage to the liver. Three cases showed evidence of liver injury but no decrease in the glucose tolerance. In four cases both glucose tolerance and liver function were normal, and in one case the glucose tolerance test was unsatisfactory. It should also be noted that in the cases with decreased glucose tolerance and evidence of damage to the liver there was no relation between the degree of liver damage and the degree of decrease in glucose tolerance.

A comparison of the liver function and the glucose tolerance is shown in Table 2. A word of explanation is necessary in regard to the "index of glucose tolerance" included in Table 2. As stated above, curves of the blood sugar concentrations following the ingestion of glucose may vary from the normal in one or more of their characteristic features. This makes it difficult to express the degree of abnormality in a single numerical expression. To solve this difficulty we have employed a method described by Lamson [15] by which the area subtended by a curve is used to express numerically the degree of abnormality of the function represented by that curve. The blood sugar concentrations were plotted on coordinate paper, ruled twenty divisions to the inch, where one-fourth ordinal inch represented 10 mg. of sugar and one-fourth abscissal inch represented five minutes. The area subtended by such a curve was measured and the figure thus obtained (square inches), when compared with the figure obtained by measuring the area subtended by a maximum "normal" curve, indicates the degree of abnormality of the glucose tolerance. This figure has been called by us the "glucose tolerance index." The method is not entirely exact as

15. Lamson, P. D.; Gardner, G. H.; Gustafson, R. K.; Maire, E. D.; McLean, A. J., and Wells, H. S.: The Pharmacology and Toxicology of Carbon Tetrachlorid, J. Pharm. & Exper. Therap. **22**:215 (Nov.) 1923.

the curves that are slightly abnormal, particularly as regards the time of maximum concentration of the blood sugar, may give figures that fall within the maximum figures of normal. It is, however, we believe, sufficiently accurate for our purpose. As stated above, a glucose tolerance index of 10 or below is considered normal in this study.

With the figures so obtained a statistical study [16] has been made of the data in Table 2 to determine further if any relation exists between the glucose tolerance, thus expressed, and the liver function.

The average of the indexes of glucose tolerance is 14.6 and the average liver function expressed in percentage of dye retained at one hour is 2.7. The standard deviation of the index of glucose tolerance is

TABLE 2.—*Comparison of Glucose Tolerance and Liver Function**

		Glucose Tolerance Blood Sugar Concentrations, Mg. Per 100 C.c.				Index Glucose Tolerance†	Liver Function‡
No.	Case	Fasting	15 Minutes	1 Hour	2 Hours		
1	5	0.083	0.111	0.174	0.166	10.3	0
2	8	0.136	0.187	0.200	0.200	16.6	0
3	9	0.110	.....	0.250	0.174	18.7	0
4	14	.....	0.136	0.187	0.120	10.4	0
5	16	0.103	0.141	.....	0.132	6.6§	0
6	18	0.096	0.226	0.186	0.100	13.2	0
7	20	0.089	0.103	0.187	0.132	9.6	0
8	27	0.136	.....	0.370	0.340	33.5	0
9	31	0.111	0.137	0.204	0.125	12.0	0
10	3	0.103	0.142	0.230	0.180	17.4	2
11	7	0.12	0.200	0.200	0.174	13.8	2
12	24	0.083	0.166	0.150	0.111	9.9	2
13	17	0.160	0.200	0.260	.....	16.3	2.5
14	21	0.077	0.125	0.217	0.172	13.8	2.5
15	12	0.100	0.200(40 min.)	0.200	0.214	14.0	12(15 min.)
16	25	0.105	0.157	0.229	0.142	14.9	3
17	29	0.111	0.192	0.192	0.190	15.6	3
18	13	0.093	0.250	0.250	0.127	20.2	4
19	23	0.080	0.120	0.176	0.118	8.9	4
20	26	0.103	0.153	0.184	0.168	12.8	4
21	28	0.120	0.136	0.161	0.111	8.5	4
22	41	0.100	0.202	0.113	0.090	7.1	—5
23	2	0.136	0.166	0.230	0.270	20.4	5
24	10	0.120	0.150	0.250	0.100	14.5	5
25	1	0.100	0.250	0.250	0.300	26.5	5
26	6	0.136	0.150	0.187	0.166	12.8	8
27	4	0.080	0.120	0.250	0.187	16.4	10
28	30		Unsatisfactory		.....	....	10

* Table is arranged in the order of increasing degree of liver injury.
† Description of the method by which this index is obtained is given in text. Ten or below is considered normal.
‡ Phenoltetrachlorphthalein method, percentage of dye retained at one hour.
§ The index in this case is misleading because of the loss of the hour specimen.

6.266 and of the liver function 2.628. The coefficient of correlation of the glucose tolerance and liver function is 0.3738 ± 0.1137.

In Figure 1 this lack of correlation is shown.[17] This figure is a scatter diagram of the deviations from the mean divided by the standard deviation of the index of glucose tolerance and of the liver function. The results are plotted against each other.

16. Hodges, P. C., and Eyster, J. A. E.: Estimation of Cardiac Area in Man, Am. J. Roentgenol. **12**:252 (Sept.) 1924.

17. Davis, H. W.; Meakins, J., and Sands, J.: The Influence of Circulatory Disturbances on the Gaseous Exchange of the Blood, V, The Blood Gases and Circulation Rate in Hyperthyroidism, Heart **11**:299, 1924.

It might be expected that some relation would be found to exist between the liver injury and the basal metabolism since it would seem natural for liver injury to occur in the more severe cases in which the metabolic rate would tend to be high. There was a slight tendency to such a relation but it was not constant. Of the twenty-two patients presenting evidence of liver damage fifteen, or 69 per cent., had a maximum basal rate of plus 50 per cent. or over. There was, however, considerable variation so that the average basal rate of plus 56.2 per

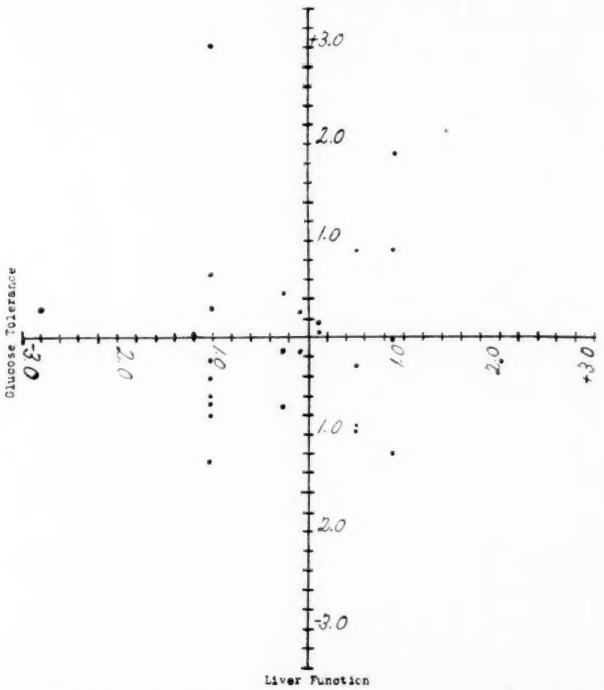


Fig. 1.—Comparison between the deviations from mean divided by standard deviation of glucose tolerance expressed as "glucose tolerance index" and liver function expressed in percentage of dye retained at one hour (from Table 2); Cases 12 and 28 have been omitted.

cent. is scarcely a true representation of the facts and several cases with a relatively low basal rate showed evidence of liver damage (Cases 28, 29, 38 and 37). Of equal importance, of the twenty-two patients without evidence of liver damage nearly as many (fourteen) had a maximum basal metabolic rate of plus 50 per cent. or over. In the case of the patients presenting evidence of liver damage no relation between the height of the metabolic rate and the degree of functional impairment of the liver was noted.

In Table 3 comparison is made between the basal metabolic rates and the test of liver function. The data in this table also have been studied statistically to determine further if any relation exists between metabolic rate and liver function. The average basal metabolic rate expressed in percentage of deviation from normal (tables of Aub and Dubois) is plus 57.1 per cent. and the average liver function, expressed in per-

TABLE 3.—*Comparison of Basal Metabolic Rate and Loss of Weight with Liver Function**

No.	Case	Liver Function †	Basal Metabolic Rate (Maximum)‡ Deviation, per Cent.	Loss of Weight (Kg.)
1	5	0	50.5	11.3
2	8	0	24.6	10.0
3	9	0	35.5	....
4	14	0	78.0	11.3
5	15	0	60.0	6.8
6	16	0	23.0	13.1
7	18	0	50.5	7.7
8	19	0	26.5	9.0
9	20	0	66.0	18.1
10	27	0	38.0	11.8
11	31	0	108.0	14.5
12	32	0	50.0	38.6
13	22	1	68.0	5.0
14	34	1	78.0	9.0
15	3	2	21.0	3.6
16	7	2	16.5	27.2
17	24	2	92.0	13.6
18	17	2.5	105.0	11.8
19	21	2.5	75.0	12.7
20	11	3	49.5	13.6
21	43	3	91.0	10.0
22	44	3	86.5	23.6
23	12	12 (15 min.)	82.0	15.0
24	36	3	16.0	....
25	25	3	61.0	13.6
26	29	3	21.0	9.0
27	37	3	25.0	....
28	13	4	64.0	4.5
29	23	4	70.0	8.1
30	26	4	77.5	11.8
31	28	4	29.0	4.5
32	33	4	63.5	20.0
33	41	5	56.0	4.5
34	2	5	36.0	9.0
35	10	5	39.5	31.8
36	35	5	54.0	4.0
37	38	5	73.5	7.2
38	39	5	44.0	7.2
39	1	5	45.7	2.7
40	42	5	72.5	4.5
41	6	8	70.0	....
42	4	10	73.0	11.8
43	30	10	70.0	18.1
44	40	10	93.0	34.0

* Table is arranged in the order of increasing degree of liver damage.
† Phenoltetrachlorphthalein method, percentage of dye retained at one hour.
‡ Percentage of deviation from normal, table of Aub and Dubois.

centage of dye retained at one hour, is 3.04 per cent. The standard deviation of the basal metabolic rate is 77.734 and of the liver function 2.814. The coefficient of correlation between basal metabolic rate and liver function is 0.2275 ± 0.0954, thus substantiating the conclusions drawn above. Figure 2 is a scatter diagram similar to Figure 1 and illustrates well the lack of correlation between basal metabolic rate and liver function.

Loss of weight was a fairly constant factor in the patients showing liver damage, as might be expected in view of the nature of the disease. Frequently it was extreme and it amounted to 9 kg. (20 pounds) or more in twenty-seven (67 per cent.) of the forty patients in whom the loss of weight was determined. Table 3 gives a comparison between the loss of weight and the test of liver function. In an earlier article [18] we stated that there was no constant relation between the loss of weight and the liver function. However, a statistical study of the data in Table 3 shows a slight correlation between these two factors. The

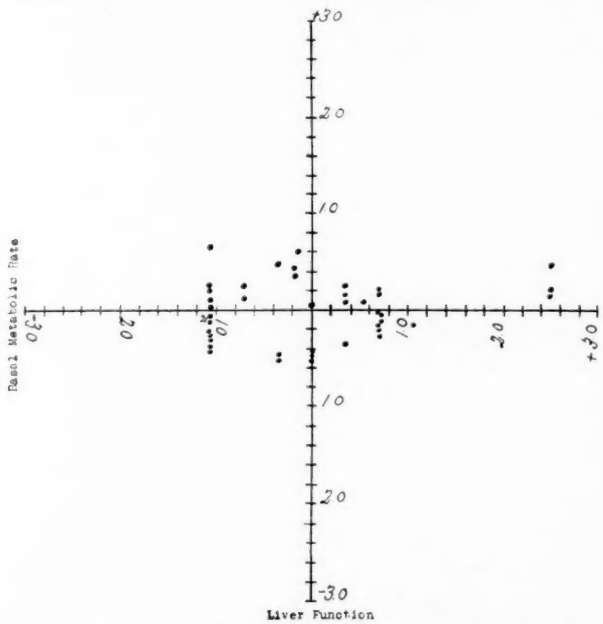


Fig. 2.—Comparison between deviations from mean divided by standard deviation of basal metabolic rate, expressed as percentage of deviation from normal, and liver function, expressed as percentage of dye retained at one hour (from Table 3); Cases 11 and 12 have been omitted.

average loss of weight in kilograms is 12.5 and the average liver function expressed in percentage of the dye retained at one hour is 3 per cent. The standard deviation of the loss of weight is 8.419 and of the liver function 2.712. The coefficient of correlation between the loss of weight and liver function, thus expressed, is 0.4257 ± 0.0873. Figure 3 is a scatter diagram similar to Figures 1 and 2 and illustrates this relation. It was noted clinically that evidence of liver injury was more

18. Warfield, L. M., and Youmans, J. B.: Tr. A. Am. Phys. **39**:130, 1924.

apt to be encountered in patients who, in addition to having lost weight, developed an inability to maintain a satisfactory caloric intake, a point that may be of some practical importance.

Early in the course of this study it was thought that possibly some connection would be established between the liver injury and the clinical type of the disease. Further work showed the fallacy of such an assumption. Unfortunately, such attempted correlation is hampered by

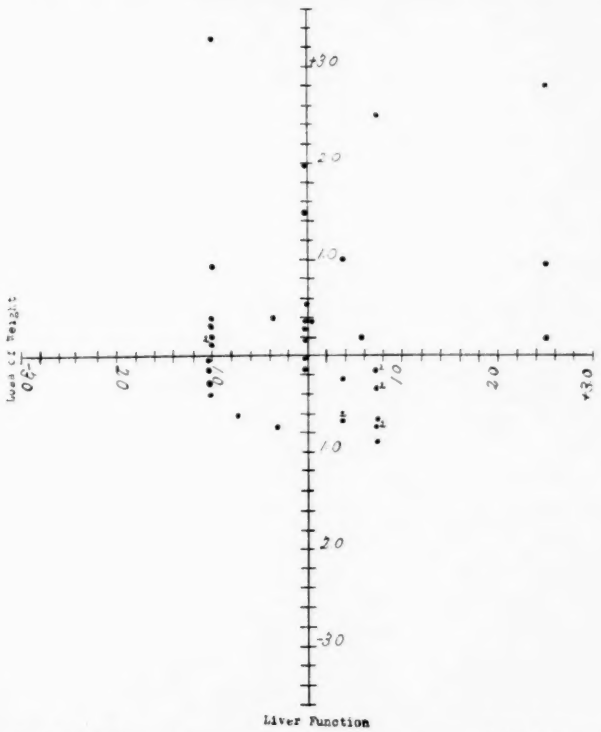


Fig. 3.—Comparison between deviations from mean divided by standard deviation of loss of weight in kilograms and liver function expressed in percentage of dye retained at one hour (from Table 3).

the lack of uniformity of classification or even of general agreement as to the exact etiology and pathology of the disease. In Table 1 it is seen that an attempt has been made to classify the various cases according to the clinical classification commonly used. Necessarily all the data used in making this classification cannot be given here. Comparison of various types so classified and the figures showing evidence of liver damage fail to show any definite association between any type of

the diseases and the presence or absence of injury to the liver. Neither was any relation apparent between the evidence pointing to liver damage and the acuteness or chronicity of the disease.

No relation between liver damage and such factors as age, sex or the usual laboratory examinations was noted, with one exception. Frank jaundice or a subicteric tint occurred in seven patients and in all but one instance occurred in the group of patients with the more severe liver damage, a fact consistent with the usual clinical interpretation of this finding.

The additional tests of liver function (levulose tolerance, hemoclastic crisis test and the determination of the concentration of bilirubin in the blood serum) were done in too few instances to warrant more than passing comment. The usual argument for the use of more than one test of the functional efficiency of the liver is based on the fact that many of these tests are tests of separate and distinct functions. It is assumed that one function might be impaired and the impairment detected without a disturbance of the other functions. We do not adhere strictly to this point of view, but it is entirely possible that the tests vary in their sensitiveness and that one of the tests might give evidence of an impaired function in spite of negative results with the other tests.

The data obtained by the various tests of liver function are shown in Table 4. In general it might be said that the levulose tolerance test failed to give evidence of impairment of liver function when present as often as did the phenoltetrachlorphthalein test. Once both were negative, and once the levulose tolerance test was positive and the phenoltetrachlorphthalein test negative. Since, as stated above, the technic of the hemoclastic crisis test used by us differs from that described by the originators, comparison between it and other methods is not warranted.

Early in this work it was noted that the serum of the blood samples following the injections of the phenoltetrachlorphthalein showed an apparent increase in the bilirubin content, an observation also made by Blum and Rosenau.[6] Later it was noted that the blood drawn previous to the injection of the dye frequently showed a similar change. We concluded that some of these patients had an increase in the serum bilirubin independent of any increase possibly due to the dye. It was therefore determined to test the amount of bilirubin in the blood serum of these patients, using for this purpose blood secured before the injection of the phenoltetrachlorphthalein. This test was made in twelve cases. The bilirubin was found increased seven times and in six of the seven cases the phenoltetrachlorphthalein test was positive. Twice it was found in normal amounts, both times associated with a negative phenoltetrachlorphthalein test. In three cases the test was unsatisfactory. These results are not surprising since jaundice occurred in three

TABLE 4.—*Comparative Data Obtained by the Various Tests of Liver Function*

Case	Phenoltetrachlorphthalein Percentage Retained Dye		Levulose Tolerance Blood Sugar Concentration Mg. Per 100 C.c.				Widal Hemoclasis Test					Icterus Index
								After Milk				
	15 Minutes	1 Hour	Fasting	15 Minutes	1 Hour	2 Hours	Fasting	30 Minutes	1 Hour	1½ Hour	2 Hours	
34	..	1	0.087	0.094	0.112	0.087	7,050	8,500	9,100	8,150	8,450	4.0
43	..	3—	0.082	0.095	0.130	0.107	6,400	7,800	7,500	.....	7,800	10.0
44	..	3—	0.088	0.105	0.115	0.104	9,200	6,200	8,000	6,900	9,700	3.0
36	..	3	0.099	0.106	0.130	0.103	5,600	6,600	8,000	8,000	.....	Serum cloudy
37	..	3+	0.101	0.103	0.122	0.103	.....	.....	.....	.....	.....	Serum cloudy
33	..	4	.....	.....	.....	.....	.....	.....	.....	.....	.....	13.6
35	..	5	.....	.....	.....	.....	5,350	4,900	3,800	4,050	5,550	9.2
38	..	5	0.096	0.131	0.127	0.111	3,400	3,400	3,350	4,200	4,000	11.4
39	..	5	.....	.....	.....	.....	.....	.....	.....	.....	.....	10.0
42	..	5	0.102	0.140	0.192	0.111	7,250	8,350	7,300	7,200	6,800	Serum lipemic
30	10	10	.....	.....	.....	.....	.....	.....	.....	.....	.....	14.2
40	..	10	.....	.....	.....	.....	2,100	2,100	3,100	2,900	9,100	21.3

cases and a subicteric tint was noted in four additional cases. Since icterus occurred it might be expected that this test, which reveals latent jaundice, would frequently be positive. These findings, we believe, offer strong additional evidence of the considerable frequency of liver damage in the cases studied since an increase in the bilirubin content of the blood serum seems to be fairly constant in cases of liver injury.[15]

An increased functional efficiency of the liver has been noted in certain stages of some diseases.[19] Usually in such cases later evidence of injury and a decreased function occur, suggesting that the first reaction of the liver to insult may be increase in its activity. An increased functional activity is difficult to detect with the tests of liver function used but it was thought that the finding of an unusually low percentage of the dye in the blood stream at the fifteen minute period, as was sometimes encountered, might be evidence of an increased function in some cases.

COMMENT

The foregoing analysis of the results would seem to warrant certain tentative conclusions. In the first place, no causal relation between liver injury and the decreased glucose tolerance of thyrotoxicosis seems to have been demonstrated. It might be argued that the glucose tolerance is itself a test of liver function and that its decrease indicates an impairment of the function of that organ. This view seems scarcely tenable to us in view of the many other factors that might affect the glucose tolerance in this disease and the absence of data in other conditions indicating such a close relation between glucose tolerance and liver function. However, although our findings fail to disclose evidence of a causal relation between liver damage and the decreased glucose tolerance in thyrotoxicosis, there is, we believe, a very definite relation between the liver damage and the disturbed carbohydrate metabolism present in this disease. A glycogen poor liver has frequently been shown experimentally in such conditions as phosphorus and chloroform poisoning to possess an increased susceptibility to injury. It has also been shown [20] that the feeding of thyroid substance or extract to animals not only causes a loss of glycogen from the liver but prevents the storage of glycogen in that organ. In addition, spontaneous glycosurias have been observed in patients treated with thyroid preparations and may indicate a disturbance in glucose tolerance similar to that occurring in thyrotoxic states. It is probable, therefore, that a change in thyroid activity in thyrotoxicosis may result in a glycogen free or poor liver,

19. Chiray, M.: L'acide Glycuronique Urinaire, Sa Valeur pour le Diagnostic de L'insuffisance Hépatique, Paris méd. **31**:359 (May 3) 1919.

20. Kuriyama, S.: The Influence of Thyroid Feeding upon Carbohydrate Metabolism, I, The Storage and Mobilization of the Liver Glycogen in Thyroid Fed Animals, J. Biol. Chem. **33**:193 (Jan.) 1918.

more susceptible to damage by some toxic agent present in this disease or more susceptible to injury by the disturbed thyroid function itself. Nor, indeed, if one may be permitted to speculate, need the conceptions of such a process be limited to the liver alone. The possible effect of such a toxic action on organs made poor in glycogen, such as the heart, at once becomes apparent. Added support is given to such an hypothesis by the well known beneficial effects of glucose in this disease.

In an attempt to throw further light on these problems we have performed some preliminary experiments in which dogs were fed thyroid extract and the effect of such feeding on liver function determined by the use of the phenoltetrachlorphthalein test. So far the results indicate that neither the feeding of large amounts over short periods of time or the feeding of small amounts over a longer period has any effect on the functional efficiency of the liver. Further work on this phase of the problem has been planned.

Practically, the significance of injury to an organ so important and of such varied functions as the liver is obvious. Further study may indicate which of, and to what extent, its various functions are involved and the relation of such injury to prognosis and therapy. Of still greater importance is the possible effect of a disturbed carbohydrate metabolism in connection with the injury to a number of important tissues and organs.

CONCLUSIONS

1. Tests of liver function have been made in forty-four patients with thyrotoxicosis. In twenty-eight of the patients tests of the glucose tolerance also were made.

2. Twenty-two, or 50 per cent., of the patients in this series showed an impairment of liver function according to the tests of liver function used. Twenty-one of the twenty-seven cases satisfactorily tested showed a decreased glucose tolerance.

3. No relation was found to exist between the functional efficiency of the liver as tested and the glucose tolerance, basal metabolic rate or other features of the disease except loss of weight.

4. The impairment of liver function in thyrotoxicosis seems to be associated to some degree with loss of weight.

HYPERGLYCEMIA

II. PHYSICAL AND CHEMICAL STUDIES OF HUMAN BLOOD FROM CASES OF DIABETES MELLITUS *

LEE FOSHAY, M.D.
Fellow in Medicine, Lakeside Hospital and Western Reserve University School of Medicine
CLEVELAND

In a previous article [1] I have discussed the relation of hyperglycemia to variation in the water content of the blood and of the body tissues. It was observed that all young diabetic patients responded to hyperglycemia by a concentration of the blood and an exsiccation of the tissues, while in arteriosclerotic diabetic patients the response was simply a dilution of the blood with little or no tissue dehydration. It emphasizes the precarious condition of the young diabetic patient, for he is not only liable to acidosis and coma as a result of deranged fat metabolism but also, because of the nonvolatile acidosis that accompanies anhydremia, he is continually suffering some diminution of the alkaline reserve of his blood plasma. Thus the young diabetic patient is always potentially in a state of acidosis. On the other hand, in the absence of factors that cause acute exacerbation, the arteriosclerotic diabetic patient is not afflicted with a nonvolatile acidosis and, for other reasons previously mentioned, does not so readily or so frequently fall a victim to diabetic coma. In the event of an acute exacerbation the arteriosclerotic diabetic patient becomes exsiccated and otherwise behaves exactly as a young diabetic patient.

In view of the fact that large differences were found in the water content of the bloods of these patients, a difference in the two large groups mentioned above and differences in the blood of any given case due to the administration of insulin, it was hoped that further means of differentiation might be afforded by a study of some of the physical and chemical properties of the blood and blood serum in serial samples taken from patients in both groups.

METHOD

The following determinations were made on each sample: Specific conductivity at 5 degrees C. of the whole blood and of the serum, chlorin in the whole blood and in the serum, glucose in the whole blood and in the serum, erythrocyte counts, and in certain instances

---

* From the department of medicine of Lakeside Hospital and Western Reserve University School of Medicine.

1. Foshay, Lee: Hyperglycemia, I, The Relative Blood Volumes in Diabetes Mellitus, Arch. Int. Med. **36**:889 (Dec.) 1925.

the plasma carbon dioxid combining power. From the foregoing data the following were calculated: the relative volumes of serum and cells, the volume of the average erythrocyte, glucose content of the erythrocytes and chlorin content of the erythrocytes.

1. *Preparation of Samples.*—Blood was drawn from an antecubital vein with the utmost care to avoid venous stasis for more than a brief moment. Part of this blood was immediately oxalated for the determination of whole blood glucose and chlorin. The remainder was carefully defibrinated in chemically clean porcelain dishes by means of thin wooden applicator sticks. By this method visible hemolysis was rare. Whenever gross hemolysis occurred, the sample was discarded.

2. *Erythrocyte Counts.*—These were made in duplicate with the same pipet and counting chamber. All counts that did not check within 250,000 per cubic millimeter were discarded. In each instance the figure given represents the average of the two counts made on the defibrinated blood.

3. *Electrical Conductivity.*—The apparatus consisted of a combined resistance box and Wheatstone bridge furnished by the Central Scientific Company, bright platinum electrodes, a variable temperature water-bath, a simple induction coil operating on dry cells, a microphone and several U tubes. The conductivity cells required about 3 c. c. of blood or serum. The cell constants were determined repeatedly throughout the course of the work by means of a standard fiftieth molar potassium chlorid solution. All determinations were made at temperatures somewhere between 5 and 10 degrees C. Temperature correction to 5 degrees C. was made in every instance by means of previously constructed tables showing the thermal coefficient of conductivity of blood serums containing various chlorin concentrations at temperatures from 0 to 30 degrees C. These tables are accurate to 0.1 degree C. For practical purposes one such table was found to be sufficient, since within the range of temperatures employed the maximal variation in chlorin concentrations caused a difference of only 0.2 $K \times 10^4$ per degree Centigrade. The same conductivity cell was always used to determine the conductivity of the whole blood and of the serum from each blood sample. After measuring the conductivity of the whole blood, the specimen was centrifugated and the procedure repeated on the serum. The results are expressed as specific conductivities, that is, $K \times 10^4$ at 5 degrees C.

4. *Relative Volumes of Serum and Erythrocytes.*—These were calculated from the conductivity measurements by means of the relation developed by Stewart.[2]

2. Stewart, G. N.: The Relative Volume or Weight of Corpuscles and Plasma in Blood, J. Physiol. **24**:356 (July) 1899.

5. *Average Erythrocyte Volume.*—The relative volume of erythrocytes in cubic millimeters divided by the number of erythrocytes per cubic millimeter gives the volume occupied by the average erythrocyte. The results are expressed as cubic microns.

6. *Glucose.*—This was determined both in the whole blood and in the serum by the method of Folin and Wu.[3]

7. *Chlorin.*—This was determined by Whitehorn's method.[4]

8. *Corpuscular Chlorin and Corpuscular Glucose Concentrations.*—These were calculated from the foregoing data according to the formula:

$$\%\text{ in cells} = \frac{\%\text{ in whole blood} - (\text{serum volume }\% \times \%\text{ in serum})}{\text{Cell volume }\%}$$

9. *Grams Glucose and Grams Chlorin per Erythrocyte.*—Calculated from the respective concentrations, relative volume of erythrocytes and erythrocyte counts from the formula:

$$\frac{\text{Grams substance per 1 cu. mm. cells} \times \text{cell volume }\%}{\text{Number of cells per cu. mm.}} = \text{Grams substance per cell}$$

ELECTRICAL CONDUCTIVITY

A study of the electrical conductivity of the whole blood and serum has led to little that is new. The conductivity of whole blood varies inversely as the concentration. It thus provides a fairly good indication of changes in blood viscosity in serial samples. The ratio of the conductivity of the serum to the conductivity of the blood $\left(\frac{Ks}{Kb}\right)$ is an index of changes in blood viscosity due entirely to increase or decrease in the number and size of the erythrocytes, particularly in serial samples of blood, since any change in the fluidity of the serum is absorbed in the ratio. Ordinarily there is a consistent relationship between the chlorin concentration and the conductivity of the serum. A serum containing 0.5 per cent. chlorin usually has a conductance of about 72×10^{-4}, and a sample containing 0.64 per cent. chlorin usually one of about 77×10^{-4}. In Cases 15 and 22 there are conductivities that are considerably higher than the respective chlorin concentrations might lead one to expect. Indeed, in Case 15 the serum conductivities are much higher than the conductivities of equivalent concentrations of sodium chlorid in pure water (Fig. 3). This discrepancy is the same whether the relative volume of serum is above or below the normal.

This phenomenon has been described before in cases of salt and water retention nephritis and is called the "conductivity chlorid discrep-

3. Folin, O., and Wu, H.: System of Blood Analysis, J. Biol. Chem. **38**:81 (May) 1919.

4. Whitehorn, J. C.: System of Blood Analysis, J. Biol. Chem. **45**:449 (Feb.) 1921.

ancy."[5] It is mentioned here to record a similar occurrence in the blood in diabetes. The cause of this discrepancy is not clear. It has been thought that a diminished protein concentration in the serum might account for it,[6] since in solutions containing salts that are highly ionized the conductance curves parallel the fluidity curves. However,

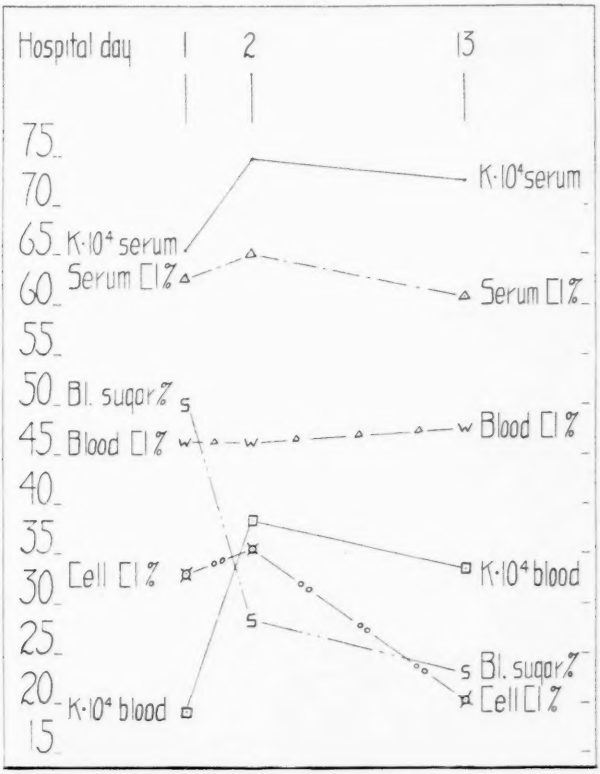


Fig. 1 (Case 33).—Blood and serum conductivities and chlorin concentrations from a case of diabetic coma, showing the changes that follow insulin administration; transient type of conductivity chlorin discrepancy present only on first day.

5. Atchley, D. W.; Loeb, R. F.; Benedict, E. M., and Palmer, W. W.: Physical and Chemical Studies of Human Blood Serum, Arch. Int. Med. **31**:606 (April) 1923.

6. Bugarsky, S., and Tangl, F.: Physikalisch-chemische Untersuchungen über die molecularen Concentrationverhältnisse des Blutserums, Arch. f. d. ges. Physiol. **72**:531 (Sept.) 1898. Palmer, W. W.; Atchley, D. W., and Loeb, R. F.: Studies in Regulation of Osmotic Pressure; Effect of Increasing Concentrations of Albumin on Conductivity of a Sodium Chlorid Solution, J. Gen. Physiol. **3**:801 (July) 1921; ibid. **4**:585 (May) 1922.

observed values have been recorded which indicate that this is not the completed explanation.[5]

In two other instances, in Cases 33 and 35, there was noted a conductivity chlorid discrepancy of the opposite nature, that is, a serum conductance much lower than the chlorin concentration would lead one to expect; but this was a transient effect in each instance, and its dis-

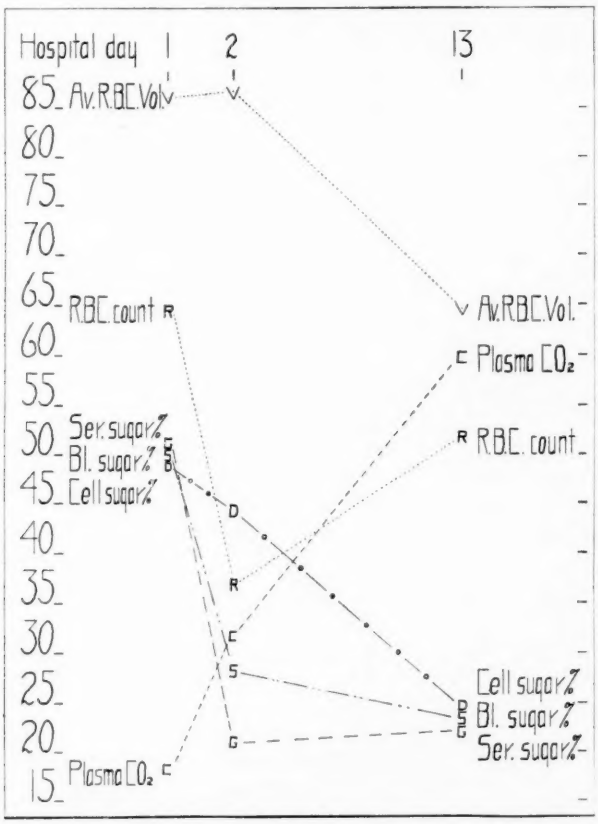


Fig. 2 (Case 33).—Average erythrocyte volume, erythrocytes per cubic millimeter, plasma carbon dioxid and glucose distribution during diabetic coma and the changes that follow insulin treatment; lag in diffusion of glucose from cells to serum as blood sugar is being reduced. (Figures 1 and 2 are from the same case as Figure 1 in Part I of the series.)

appearance after the relative blood volumes were restored to normal indicates that in this type of discrepancy the depression of the conductivity was actually a function of the fluidity of the solvent (Fig. 1). Many observers have shown that the addition of a nonelectrolyte to an

electrolytic solution will depress the conductivity.[7] Javal and Boyet[8] state that urea will not do so when added to blood serum. This appears to be true in Case 34, in which the urea concentrations were high.

WATER TRANSFERENCE BETWEEN SERUM AND ERYTHROCYTES

The normal volume of the average erythrocyte has been found to be approximately 76 cubic microns. This was determined from the bloods of thirteen normal subjects in the resting state by means of erythrocyte counts and the relative volume of cells measured by the electrical method. As the standard deviation of this series was $3.4\mu^3$ with a probable error of $\mp 2.3\mu^3$, it was not deemed necessary to examine a larger number of blood samples.

From the data in Table 1 it is seen that, at the time of admission to the hospital, all young diabetic patients and two of the arteriosclerotic diabetic patients with acute exacerbations (Cases 14 and 21) had very large erythrocytes, averaging from 85 to 90 cubic microns. If the patient died, the volume remained stationary at subsequent examinations, but with recovery of the patient the size of the erythrocytes returned to normal. With the exception of the two patients mentioned above, one of whom died, all of the arteriosclerotic diabetic patients behaved differently, even in the presence of acute exacerbations of symptoms. In these patients there was no increase in the erythrocyte volume even in the presence of hyperglycemia up to 0.53 per cent. (Cases 1, 10, 13, 15, 22 and 26).

Thus, in comparing these two groups of diabetic patients, those without and those with advanced arteriosclerosis, there is a marked disparity in the manner in which the erythrocytes respond to the changes induced by hyperglycemia. In the patients of the first group the erythrocytes imbibe water and increase their volume, while in those of the second group there is apparently no water transference.

Persistent macrocytosis or microcytosis has been described as a characteristic feature of a wide variety of diseases. Probably the macrocytosis of pernicious anemia and the microcytosis of chronic posthemorrhagic secondary anemia are the best known examples. Transient changes in the size of the erythrocyte are not characteristic of any disease entity but have been observed only when the blood p_H or the alkaline reserve of the plasma has been altered either by natural process, by morbid process or by experimentation. Thus Price-Jones[9] observed the diurnal variation in the size of the erythrocyte in normal

7. Kraus, C. A.: The Properties of Electrical Conducting Systems, New York, 1922, p. 121.

8. Javal and Boyet: Variations de la Conductibilite electrique du Serum Sanguin, Compt. rend. Soc. de biol. **68**:442 (March) 1910.

9. Price-Jones, C.: The Diurnal Variations in the Size of the Red Blood Cells, J. Path. & Bacteriol. **23**:371 (Dec.) 1920.

TABLE 1.—*Physical and Chemical Determinations on Blood from Diabetic Patients*

Case	Date	K × 10⁴ at 5° C.		Per Cent. by Volume		Glucose				Chlorin				Red Blood Cells per C.Mm., Millions	Volume of Average Red Blood Cells, Cubic Microns	Plasma Carbon Dioxid, per Cent. by Volume
		Blood	Serum	Serum	Cells	Blood, per Cent.	Serum, per Cent.	Cells, per Cent.	Cells, Gm. × 10^{-12}	Blood, per Cent.	Serum, per Cent.	Cells, per Cent.	Cells, Gm. × 10^{-12}			
1	11/23/23	34.4	74.5	64.4	35.6	0.53	....	.....	.....	0.420	0.580	0.130	0.100	4.700	75.8	42.0
	11/26/23	41.3	77.2	70.9	29.1	0.15	....	.....	.....	.....	.....	.....	.....	.....	.....	50.0
	12/15/23	43.7	79.1	72.0	28.0	0.14	....	.....	.....	.....	.....	.....	.....	3.800	73.7	....
10	4/30/24	30.6	76.8	57.1	42.9	0.33	....	.....	.....	.....	0.643	.....	.....	5.595	76.7	....
	5/10/24	31.7	78.8	57.2	42.8	0.18	....	.....	.....	.....	0.676	.....	.....	5.700	75.1	....
13	4/18/24	32.6	75.7	60.8	39.2	0.30	....	.....	.....	.....	0.627	.....	.....	4.995	78.5	....
	4/22/24	31.7	76.1	59.2	40.8	0.27	....	.....	.....	.....	0.610	.....	.....	6.195	65.9	....
	4/30/24	33.0	75.0	62.0	38.0	0.17	....	.....	.....	....	0.593	.....	.....	5.090	74.7	....
	5/10/24	29.3	77.9	54.4	45.6	0.26	....	.....	.....	.....	0.627	.....	.....	5.920	77.1	....
14	4/20/24	26.6	71.9	54.5	45.5	0.35	....	.....	.....	0.400	0.594	0.209	0.257	5.330	85.8	16.4
	4/21/24	34.5	76.9	62.6	37.4	....	....	.....	.....	.....	0.659	.....	.....	4.215	88.8	....
	4/22/24	28.6	74.3	55.9	44.1	0.60	....	.....	.....	.....	0.651	.....	.....	5.355	82.4	12.5
15	5/ 5/24	21.6	73.5	44.7	55.3	0.40	....	.....	.....	0.300	0.528	0.155	0.087	7.350	75.3	58.0
	5/ 7/24	31.0	80.1	55.5	44.5	0.17	....	.....	.....	.....	0.594	.....	.....	5.810	76.6	....
	5/10/24	31.9	77.2	58.7	41.3	0.16	....	.....	.....	.....	0.561	.....	.....	5.570	74.2	....
	5/14/24	32.4	80.0	57.4	42.6	0.17	....	.....	.....	.....	0.709	.....	.....	5.120	83.2	....
	5/19/24	30.0	76.1	56.8	43.2	0.24	....	.....	.....	.....	0.577	.....	.....	5.700	75.7	....
	5/23/24	37.9	81.4	63.8	36.2	0.17	....	.....	.....	.....	0.551	.....	.....	5.920	61.1	....
20	5/23/24	26.5	73.0	53.6	46.4	0.43	....	.....	.....	0.350	0.561	0.106	0.092	5.350	86.7	46.6
21	5/20/24	23.9	73.9	48.6	51.4	0.37	...	.....	.....	0.350	0.610	0.105	0.084	6.420	80.1	....
	6/11/24	26.3	73.2	52.5	47.5	0.20	....	.....	.....	0.360	0.592	0.104	0.091	5.450	87.3	....
	6/18/24	28.3	74.8	55.1	44.9	0.18	...	.....	.....	0.447	0.627	0.226	0.170	5.970	75.2	....
22	6/ 8/24	37.5	80.5	63.6	36.4	0.07	....	.....	.....	0.490	0.577	0.338	0.226	5.440	66.9	....
	6/13/24	36.9	75.6	67.0	33.0	0.15	....	.....	.....	0.478	0.660	0.109	0.077	4.670	70.7	....
	6/17/24	33.0	76.1	61.1	38.9	0.21	....	.....	.....	0.495	0.660	0.236	0.184	4.980	78.1	....
23	6/ 8/24	30.7	76.1	57.9	42.1	0.20	....	.....	.....	0.370	0.599	0.055	0.048	4.800	87.7	....
	6/13/24	33.4	73.2	64.2	35.8	0.18	....	.....	.....	0.462	0.643	0.137	0.122	3.900	89.1	....
	6/17/24	33.5	73.2	64.2	35.8	0.38	....	.....	.....	0.478	0.594	0.270	0.224	4.300	83.1	....

24	6/10/24	30.7	72.2	60.9	39.1	0.14	....	.....	.....	0.460	0.574	0.282	0.164	6.730	58.1	....
	6/17/24	32.2	73.5	62.0	38.0	0.12	....	.....	.....	0.447	0.627	0.153	0.110	5.450	69.7	....
25	6/10/24	32.3	74.8	61.1	38.9	0.13	....	.....	.....	0.440	0.595	0.197	0.124	6.170	63.1	....
	6/18/24	33.2	74.8	62.5	37.5	0.16	....	.....	.....	0.495	0.627	0.275	0.205	5.020	74.7	....
26	6/10/24	29.5	74.8	57.0	43.0	0.17	....	.....	.....	0.440	0.620	0.202	0.129	6.740	63.9	....
	6/17/24	27.5	71.5	56.3	43.7	0.22	....	.....	.....	0.420	0.447	0.198	0.143	6.080	72.0	....
28	6/10/24	30.0	74.5	58.0	42.0	0.24	....	.....	.....	0.460	0.641	0.210	0.160	5.210	80.7	....
	6/17/24	32.7	74.5	62.0	38.0	0.22	....	.....	.....	0.412	0.643	0.025	0.020	4.840	78.5	....
29	6/10/24	31.4	74.5	60.2	39.8	0.16	....	.....	.....	0.490	0.598	0.327	0.251	5.190	76.7	....
	6/17/24	33.2	74.9	62.4	37.6	0.14	....	.....	.....	0.495	0.660	0.221	0.171	4.840	77.6	....
30	6/11/24	29.4	72.2	58.9	41.1	0.26	....	.....	.....	0.360	0.560	0.074	0.057	5.360	76.8	....
	6/18/24	28.9	72.2	58.8	41.2	0.24	....	.....	.....	0.447	0.643	0.168	0.147	4.720	87.4	....
33	9/11/24	19.3	66.7	44.7	55.3	0.50	0.50	0.499	0.428	0.462	0.626	0.330	0.283	6.450	85.8	18.0
	9/12/24	37.8	74.0	69.5	30.5	0.28	0.21	0.439	0.378	0.462	0.649	0.360	0.310	3.545	86.1	31.5
	9/23/24	34.8	72.5	66.8	33.2	0.23	0.23	0.230	0.148	0.478	0.610	0.212	0.136	5.155	64.4	60.0
34	9/23/24	50.6	72.8*	84.8	15.2	0.08	0.05	0.246	0.153	0.528	0.610	0.072	0.045	2.445	62.3	....
	9/26/24	48.5	70.8‡	86.0	14.0	0.38	0.33	0.686	0.337	0.577	0.627	0.270	0.133	2.855	49.1	12.7
35	7/ 5/24	14.5	60.8	38.2	61.8	0.15	0.17	0.138	0.116	0.505	0.700	0.385	0.324	7.230	84.2	....
	7/ 7/24	20.5	63.1	49.8	50.2	0.13	0.12	0.140	0.123	0.340	0.503	0.218	0.192	5.700	88.1	....
	7/10/24	34.9	71.1	68.3	31.7	0.09	0.008	0.076	0.053	0.478	0.633	0.144	0.100	4.570	69.4	....
	7/13/24	38.2	75.0	69.1	30.9	0.07	0.10	0.030	0.017	0.495	0.660	0.125	0.071	5.450	56.6	....
36	11/20/24	21.1	76.6	42.2	57.8	0.38	0.42	0.35	0.277	0.400	0.640	0.225	0.178	7.310	79.1	14.5
37	11/26/24	28.8	77.1	54.2	45.8	0.21	0.22	0.198	0.147	0.428	0.652	0.163	0.122	6.160	74.4	....
		28.9	76.7	54.7	45.3	0.23	0.25	0.205	0.167	0.430	0.627	0.192	0.156	5.560	81.5	....
		27.9	75.4	54.2	45.8	0.21	0.17	0.257	0.205	0.412	0.627	0.158	0.122	5.740	79.8	....
38	12/ 4/24	29.4	73.6	57.7	42.3	0.25	0.27	0.22	0.179	0.462	0.611	0.259	0.210	5.210	81.2	....
		32.6	75.0	61.4	38.6	0.25	0.28	0.20	0.135	0.462	0.640	0.179	0.121	5.710	67.6	....
		29.6	72.8	58.8	41.2	0.30	0.27	0.34	0.269	0.462	0.611	0.129	0.102	5.220	79.0	....
		29.9	74.7	56.4	43.6	0.23	0.21	0.23	0.169	0.462	0.528	0.377	0.276	5.950	73.3	....
39	2/ 4/25	30.0	71.4	60.5	39.5	0.27	0.28	0.26	0.207	0.460	0.627	0.205	0.164	4.955	79.8	....
		29.5	70.9	60.1	39.9	0.26	0.28	0.22	0.190	0.460	0.601	0.248	0.214	4.630	86.2	....
		28.6	70.0	59.6	40.4	0.21	0.26	0.126	0.108	0.478	0.594	0.307	0.264	4.700	85.9	....
		29.2	71.4	59.4	40.6	0.23	0.23	0.240	0.217	0.478	0.626	0.261	0.236	4.485	90.5	....

* Blood urea, 224 mg. per hundred cubic centimeters.
‡ Blood urea, 187 mg. per hundred cubic centimeters.

men and correlated the changes in size with variation in the reaction of the blood. Dautrebande and Davies [10] noted an increase in erythrocyte volume following violent exercise. I have repeatedly found erythrocytes with volumes ranging from 90 to 97 cubic microns in cases of nephritic acidosis and in lobar pneumonia, and many observers have found experimentally that adding carbon dioxid, lactic acid, hydrochloric acid and other acids to blood causes an increase in the volume of the erythrocytes.

Mellanby and Wood,[11] working with carbon dioxid on sheeps' blood, have shown that this reaction is reversible. If blood saturated with carbon dioxid and containing swollen erythrocytes is allowed to stand for a period of hours, the volume of the erythrocytes gradually diminishes and eventually returns to normal. Now, in the young diabetic patient, if this increase in volume is due wholly to increased carbon dioxid tension, it seems remarkable that such large erythrocytes should ever be found in samples of defibrinated blood, since the process of defibrination would be expected to facilitate greatly the reversal of the reaction. Yet Case 33 shows an increase in volume 33 per cent. greater than the volume finally obtained, and Case 35 shows an increase of 55 per cent. These observations were made on defibrinated blood. In the former case it is possible that carbon dioxid, the ketone acids, lactic acid and other ether-insoluble acids, such as oxyproteic acid, have combined to cause the water transfer. Whatever may be the cause of the decrease in the p_H of the blood, it seems probable that acids other than carbon dioxid are operative in producing this effect. In the latter case, which was not diabetic but a case of extreme exsiccation and temporary anuria resulting from the persistent vomiting and diarrhea of acute food poisoning, the diminished p_H was probably due not only to abnormal organic acids but also, because of the anuria, to retained inorganic acids. This case is included in the table because in all respects, the glucose concentration excepted, it is identical with Case 33, a case of typical diabetic coma.

It is interesting to note that even with a marked change in corpuscular volume there may be no change at all in the corpuscular chlorin concentration. This is in accord with the observations of Van Slyke, Wu and McLean,[12] who found that the reaction occurs regardless of the chlorin shift, which apparently has nothing to do with the total osmotic changes.

---

10. Dautrebande, L., and Davies, H. C.: A Study of the Chlorin Interchange Between Corpuscles and Plasma, J. Physiol. **57**:36 (Dec.) 1922.

11. Mellanby, J., and Wood, C. C.: The Influence of Carbon Dioxid on the Interchange of Ions Between the Corpuscles and the Serum of Blood, J. Physiol. **57**:113 (March) 1923.

12. Van Slyke, D. D.; Wu, H., and McLean, F. C.: Studies of Gas and Electrolyte Equilibria in the Blood, V, Factors Controlling the Electrolyte and Water Distribution in the Blood, J. Biol. Chem. **56**:765 (July) 1923.

Table 2 shows the average erythrocyte volume, the average number of erythrocytes and the average relative volume of erythrocytes found in this series of diabetic patients. The same data from normal adult males are included for comparison.

To summarize, the order of events in diabetes would seem to be somewhat as follows: In young patients hyperglycemia produces a dehydration of the blood and of the fixed tissues, thus causing a non-volatile acidosis with consequent increase in erythrocyte volume by reason of water transference. This may be considered the predisposing cause of diabetic acidosis. As cellular metabolism becomes more and more abnormal there is a production of ketone acids in increasingly larger amounts; this further diminishes the plasma alkaline reserve. This might be called the exciting cause of diabetic acidosis. In cases of severe acidosis with rapid onset, no doubt both processes become important factors.

In elderly, arteriosclerotic patients, hyperglycemia does not result in dehydration and acidosis; hence no water transference from the

TABLE 2.—*Averages of Relative Volumes, Numbers and Sizes of Erythrocytes in this Series of Patients*

	Average Red Blood Cells, Volume in Cubic Microns	Average Red Blood Cells, per C.Mm. Millions	Average Relative Volume of Cells, per Cent.
Young diabetic patients	84.0	5.700	47.8
Arteriosclerotic diabetic patients	73.6	5.300	39.0
All diabetic patients after establishment of constant relative blood volumes	73.0	5.200	38.0
Normal adult males	76.0	5.470	41.6

plasma to the erythrocytes and no increase in erythrocyte volume occur. The patients live in relative comfort and are not in constant danger of acidosis and coma. If a serious dietary indiscretion or acute infection supervenes, then dehydration, acidosis and coma occur just as in the young diabetic patient.

DISTRIBUTION OF GLUCOSE BETWEEN SERUM AND ERYTHROCYTES

There has been much controversy over the question whether glucose is present within the erythrocyte or not. The conclusive experiments of Ege, Gottlieb and Rakestrow [13] leave little doubt as to its presence in variable quantities, depending entirely on the glucose concentration in the plasma (Fig. 2).

In a number of cases the corpuscular glucose was determined both directly and by calculation. Changes in the concentration measured by

13. Ege, R.; Gottlieb, E., and Rakestrow, N.: The Distribution of Glucose Between Human Blood Plasma and Red Corpuscles and the Rapidity of Its Penetration, Am. J. Physiol. **72**:76 (March) 1925.

the two methods were always homodirectional in successive samples, but the figure obtained by the direct method was always too high because of the impossibility of obtaining the cells entirely free from serum. This made it impossible to check the figures against the blood

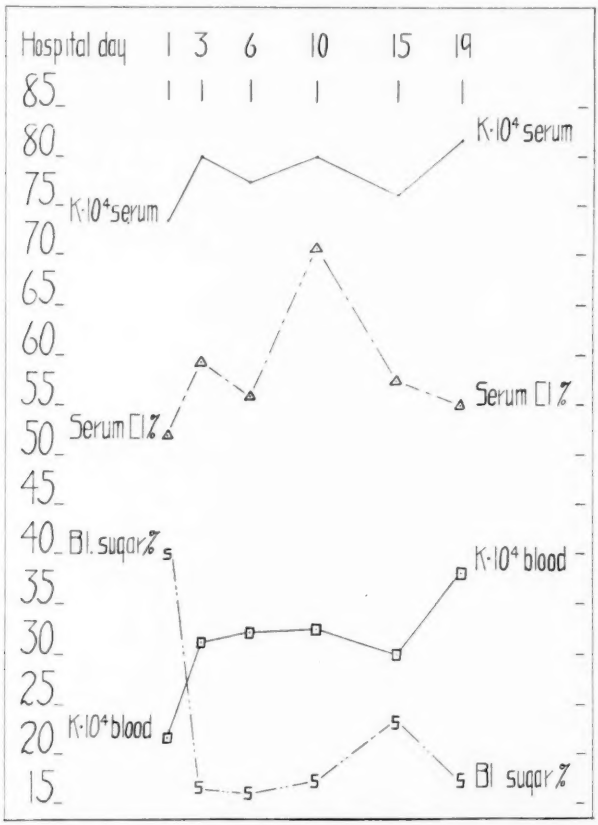


Fig. 3 (Case 15).—Blood and serum conductivities, serum chlorin concentration and blood sugar from case of diabetic coma; persistence of conductivity chlorid discrepancy. (The data are from the same case as Figure 2 in Part I of this series.)

and serum sugars, so that the method was discarded in favor of the more accurate calculation.

In general the corpuscular glucose is usually a little less than the concentration in the serum. However, as previously found in dogs,[14]

14. Foshay, Lee: Observations Upon the Action of Insulin on the Blood, with Special Reference to the Cause of the Condition Known as Hypoglycemia, Am. J. Physiol. **73**:470 (July) 1925.

with a steadily increasing hyperglycemia, by far the greater portion of the glucose is found in the serum and, conversely, with a steadily diminishing glycemia the major portion of the glucose is in the cells. The diffusion lag seems to be shorter in duration than it is in the dog.

Occasionally, if the transfer of water from the serum to the erythrocytes, or vice versa, has been large, the figures for corpuscular glucose concentration become somewhat misleading. For instance in Case 34 the corpuscular glucose concentration increased from 0.246 to 0.686 per cent., almost a threefold increase, whereas the actual quantity of glucose increased from 0.153 to 0.337 $\times$ 10^{-12} gm., a trifle more than a twofold increase. The discrepancy is due to the diminution in the volume of the erythrocytes as a result of water loss. Again, in Case 39 in the first sample the corpuscular glucose concentration is 0.26 per cent. and falls to 0.24 per cent. in the fourth sample. As a matter of fact the quantity of corpuscular glucose had risen from 0.207 to 0.217 $\times$ 10^{-12} gm. Here the apparent decrease in concentration is really only a dilution of a larger amount of glucose by means of water imbibition.

The characteristic effect of insulin on the distribution of glucose between serum and erythrocytes is well shown by a comparison of the glucose concentration of the blood, serum and cells in Case 39. This remarkable effect has been studied and reported elsewhere.[14]

THE CONCENTRATION OF CHLORIN IN THE BLOOD AND IN THE SERUM, AND THE DISTRIBUTION OF CHLORIN BETWEEN SERUM AND ERYTHROCYTES

Normally the concentration of chlorin is about 0.48 per cent. in the blood, 0.61 per cent. in the serum, and from 0.3 to 0.31 per cent. in the erythrocytes.[15] These are subject to extremely wide variations even in health. The only constant finding in diabetes is that in the presence of hyperglycemia the chlorin concentration in the whole blood is always diminished, averaging 0.37 per cent. in the initial samples of blood from severe cases. This loss of chlorin is not borne equally by the serum and the erythrocytes. In most cases the greater reduction occurs in the cells. However, in the severest cases of diabetic coma the corpuscular chlorin is either within normal limits or definitely increased, as in Cases 14, 33 and 36.

If whole blood is subjected to an increasing carbon dioxid tension, or if certain other acids are added, there is a transference of chlorin from the serum into the erythrocytes. Despite osmotic inequality on the two sides of the cell membrane, the chlorin is held in the cells by

15. Norgaard, A., and Gram, H. C.: The Relation Between the Chlorid Content of the Blood and Its Volume Per Cent. of Cells, J. Biol. Chem. **49**:263 (Dec.) 1921.

virtue of the restraint imposed on the membrane by the nondiffusible cations, chiefly Na^+ and K^+.[16]

Dautrebande and Davies[10] found that in vitro it was necessary to add sufficient acid to neutralize all the blood bicarbonate before there was any appreciable chlorin tranfer. They point out, however, that with an acidosis in vivo it is obvious that reduction of the bicarbonate reserve would cause transference to occur more readily when the blood becomes venous, because under such conditions the available alkali combined with proteins is diminished. Thus on *a priori* grounds one would expect to find a material increase in corpuscular chlorin only in the severe cases of diabetic acidosis.

A consistent relationship between hyperglycemia and corpuscular chlorin has not been found, although the results in Cases 23, 24, 29, 33 and 34 suggest the possibility. If so, this appears to offer further support to the idea that in young diabetic patients the blood alkalinity varies inversely as the glucose concentration. The failure to obtain a consistent relationship may be due to the fact that all of these patients were treated with insulin, which causes rapid changes to occur in the distribution of glucose, chlorin and water. In hyperglycemic dogs the corpuscular chlorin concentrations parallel the blood sugar curves, but after insulin has been given the comparative results are very irregular.[17] So in patients the relative concentrations found in any sample of blood depend largely on the conditions that existed prior to the administration of insulin and on the interval of time that may have elapsed between the injection of insulin and the collection of the blood. When serial specimens are collected carefully with the same time interval after insulin and food, as in Case 33, then the diminution in the relative volume of serum, depression of the specific conductivity of the serum, increase in the corpuscular volume, increased corpuscular glucose and chlorin, and diminished alkaline reserve all show simultaneous reversals as a result of the action of insulin (Figs. 1 and 2).

The same discrepancy is noted between the chlorin concentration in the erythrocytes and the actual amounts of chlorin per erythrocyte as was previously described for glucose. The reason for the discrepancies is the same, namely, the transference of water between the serum and the erythrocytes.

SUMMARY

In the two types of "conductivity chlorid discrepancy" in diabetes, one type is usually permanent, the other always transient.

16. Van Slyke, Wu and McLean (Footnote 12). Donnan, F. G.: The Theory of Membrane Equilibria, Chem. Rev. **1**:73 (April) 1924.

17. Foshay, Lee: The Relation of Hyperglycemia to the Relative Blood Volume, Chlorin Concentration and Chlorin Distribution in Dog's Blood, J. Exper. Med. **42**:89 (July) 1925.

In young, untreated diabetic patients there is evidence of some diminution of the blood alkalinity at all times. This rapidly disappears under insulin treatment.

In untreated, arteriosclerotic diabetic patients there is no evidence of diminished blood alkalinity unless the patient is nearly in coma.

In the case of extreme exsiccation from water deprivation given here, the blood picture is shown to be similar to that which occurs in acute diabetic coma. The chief differences are the greater retention of inorganic salts and a lesser glycemia.

THE PECULIAR FORMS OF INFECTION CAUSED BY THE BACILLUS OF TYPHOID FEVER

ANASTASIUS LANDAU, M.D.
Director of the First Department of the Wola Hospital
AND
M. FEJGIN, M.D.
WARSAW, POLAND

Typhoid fever is perhaps one of the best studied diseases as regards pathogenesis, the clinical course and the anatomic changes that it causes. Thanks to the bacteriologic and biologic methods of investigation, however, we have found that it can take ever so many clinical forms and that it may simulate many morbid conditions. We also must state that it is necessary to make a strict distinction between typhus abdominalis proper and other infections caused by the bacillus of Eberth.

Typhoid fever is a general infection of the blood, Schotmüller's bacteriemia. Its localization in the lymphatic system of the alimentary tract is secondary and constant but not the only one possible. There are cases of typhoid starting with symptoms indicating the inflammation of the meninges, the kidneys or the lungs in which the presence of the Eberth bacillus in the blood is bacteriologically confirmed; the typical symptoms of typhus abdominalis, roseola, the characteristic behavior of the pulse and the temperature, the intestinal symptoms, etc., appear only in its further clinical course. French authors call this condition meningotyphus, nephrotyphus and pneumotyphus. On the other hand, we see cases in which we fail to note any lesions of the lymphatic system or of the mucous membrane of the intestines with a positive result of the hemoculture and a positive Widal reaction, indicating the presence of the Eberth infection. Consequently, we must separate the typical typhoid fever from other infections that give a positive Widal reaction and an Eberth bacteriemia without the characteristic clinical symptoms and anatomic changes of typhoid.

Recently, we had an opportunity to observe in our wards a few cases of typhoid infection in various localizations entirely devoid of the clinical picture of typhus abdominalis, and probably without its characteristic anatomic changes.

REPORT OF CASES

CASE 1.—A woman, aged 33, unmarried, who had never borne children, complained of a cough with expectoration for the last fourteen days, a temperature reaching 38-39 C., stomach trouble with vomiting, and constipation. She thought that her trouble had begun after eating some cold meat. Twelve years before she had had typhus abdominalis; five years before, an influenza with pneumonia; one year before, she had undergone an operation for the removal of the appendix.

On physical examination a distinct yellowish tinge of the eyes and the skin was found. There was a dulness with harsh breath sounds over the right apex, profuse dry crepitations in both lungs, and humid râles of a very fine character from the angle of the left scapula and from the horizontal nipple line downward. There were no changes in the heart. The pulse was 84, fairly full and regular. The liver was palpable 1 cm. below the rib arch, soft and slightly painful on pressure; pressure of the right lumbar region caused pain.

In the urine, specific gravity was 1.026; there was 0.06 per cent. of albumin, and there were traces of urobilinogen. Bile acids and bile pigments were absent; the diazoreaction was negative. In the sediment there were from 30 to 40 white cells and from 1 to 3 red cells on the field, endothelial cells from the upper urinary tract, and from 1 to 2 granular casts.

The stools were formed and brown; on examination under the microscope no red or white cells were present; the guaiac and benzidin tests were negative; hydrobilirubin was present.

The blood count revealed: red cells, 3,920,000 per cubic millimeter; white cells, 7,600; platelets, 226,000 per cubic millimeter; hemoglobin, 74 per cent. The differential count was: polymorphonuclear neutrophils, 74 per cent.; lymphocytes, 23 per cent.; transitionals, 2 per cent., and Türck's forms, 1 per cent. The direct van den Bergh test in the serum was positive after twenty minutes; the indirect gave 2.5 units of bilirubin. The Widal reaction in the serum was positive with the typhoid and the paratyphoid C bacillus in a dilution of 1:400.

During the first week after the patient's admission to the hospital, the temperature oscillated between 37 and 38 C.; afterward it was normal with only slight oscillations from time to time.

The symptoms in the respiratory tract and the jaundice passed speedily during the third week. The pyelitis, however, was obstinate and yielded only after two intramuscular injections of milk, which caused a well defined reaction; namely, a rising of the temperature to 39.2 after the first injection and to 39.8 after the second. After seven weeks the patient was discharged almost completely recovered, a few white cells and an occasional endothelial cell in the sediment of the urine being the only traces of the pyelitis.

This case is interesting on account of the peculiar course of the infection, the nature of which there was no doubt as the Widal test was positive. In the absence of all clinical symptoms of typhoid fever, there was only the multilocular and characteristic localization of the infection, which attacked at the same time the liver (the parenchymatous jaundice), the respiratory tract (broncholitis sinistra inferior) and the kidney (pyelitis dextra). As these organs are the site of election for the Eberth bacillus, we felt that we had a typhoid fever infection and were inclined to make the Widal test.

Of course in this case we do not speak of typhus abdominalis; the lymphatic system of the alimentary tract was not clinically, nor to all appearances anatomically, affected. It was a typical infection, having its seat in many organs and caused by the bacillus of typhoid fever, perhaps in conjunction with *Bacillus paratyphosus* C. It also was impossible to decide, on account of the altered conditions of resistance, whether the morbid process arose in a typhoid carrier (the patient had had typhoid fever twelve years before) or if we had to do with a quite new infection independent of the infection twelve years before.

CASE 2.—A woman, aged 48, with a rather unexpected localization of typhoid fever infection, complained of frequent stools, from twenty to thirty in twenty-four hours, with very distinct traces of blood, tenesmus, and pain in the lower part of the abdomen and in the left side. She said that she had been feverish. She attributed her trouble to a fall downstairs three days before. She had fainted on falling, and afterward felt a passing pain in the left side and in the lower part of the abdomen. She had never been ill before, had borne eight children, and had had no abortions.

On physical examination no changes were noticed, except a slight roughness of the breath sounds over the right apex and a slight pulsation in the jugular vein. The lower part of the abdomen was distended, and the right iliac region was a little painful. The spleen was palpable; the succussion of the left kidney, painful. A catheter specimen of the urine showed a trace of albumin, and on inspection under the microscope from 4 to 8 white cells in each field. A slight trace of blood and mucus appeared macroscopically in the stools. The Widal reaction was positive in a dilution of 1 : 400. On the eighth and ninth day of her stay in the hospital, the temperature, which until then had been about 37.6 C., rose to 38 and afterward fell to normal. The intestinal symptoms passed entirely by the end of the first week, and after two more weeks the patient was discharged, recovered.

We had here also, no doubt, an infection produced by the Eberth bacillus, under the form of an acute hemorrhagic inflammation of the large bowel, and an inflammation of the kidney pelvis (enteritis and pyelitis typhosa), all without any clinical symptoms of typhus abdominalis.

To another group belong the cases of the Eberth bacillus infection that begin with a picture of a grave gallbladder and bile duct infection, a severe jaundice, high temperature and peritoneal symptoms, and in the further course are complicated by bronchopneumonia, the high temperature curve and bed sores. This group of cases often resembles the grave forms of typhus abdominalis, the more as we find in them either the typhoid bacillus in the blood (bacteriemia typhosa) or a positive Widal reaction in high dilution.

That we ought not to consider all these cases as typhoid fever but only as an infection with its primary seat in the liver and the gallbladder was proved by the following case.

CASE 3.—A woman, aged 27, was admitted, March 31, 1924, complaining of attacks of pain in the region of the liver, recurring in the last five days several times in twenty-four hours, with jaundice and constipation. In 1914, she suffered from similar pain, without jaundice or temperature. In 1915, she had typhoid fever. In 1920, she had a return of the pain for eight weeks, and for the last year she had similar pains but with vomiting. She was married and had had four deliveries: three of the children died, one immediately after, one a few days after, and one a few weeks after birth. There was one living child.

Physical examination revealed a distinct yellowish tinge of the skin and the sclerae; a rather dry and furred tongue; a weakness of the fremitus and breathing over the lower part of the right lung; twenty-six respirations in one minute; the heart sounds rather loud and clear; pulse, 120; a tension of the skin and painfulness on pressure in the right half of the abdomen; the right liver lobe reaching the horizontal navel line, very painful on pressure; the spleen not painful and palpable on percussion from the ninth rib.

Analysis of the urine revealed: albumin 1.5 per thousand; bile pigments, urobilinogen and urobilin, present; bile acids, absent; diazoreaction, negative; in the sediment of the urine from 20 to 30 white cells in each field and from 5 to 6 granular casts.

The blood count was: hemoglobin, 80 per cent.; red cells, 4,000,000; white cells, 19,500, and platelets, 250,000 per cubic millimeter. The differential count was: polymorphonuclear neutrophils, 90 per cent.; lymphocytes, small and middle, 4 per cent.; large, 5 per cent.; transitionals, 1 per cent. Polymorphonuclear eosinophils were not found. Bleeding time was three minutes; coagulation time, seventeen minutes. Cholesterin in the serum was 1.98 per thousand. The direct test of van den Bergh in the serum was immediate and decidedly positive; the indirect, 8 units of bilirubin. The test for resistance of the red cells showed hemolysis in 0.26 per cent. of sodium chlorid while the control showed hemolysis in 0.36 per cent. A pure culture of Eberth bacilli, identified at the state epidemiologic institute, was received from the blood; the Widal reaction in the serum with the typhoid and the paratyphoid C bacillus was positive only in a dilution of 1:50. The stools were discolored; the sublimate test was negative; the blood test was negative.

During the next few days very distinct peritoneal symptoms appeared in the region of the upper right quadrant of the abdomen, simultaneously with a dulness and an evident weakness of the breathing sounds over the lower part of the right lung, posteriorly, and over the middle lobe in the front.

As the results of several exploratory punctures of the pleura at this point were negative and the symptoms were increasing, we thought of a subphrenical

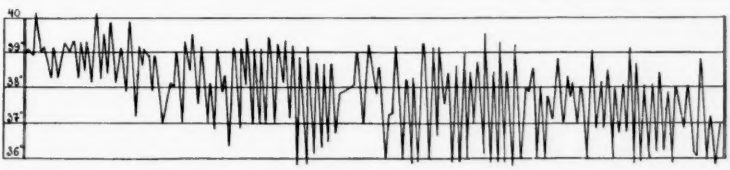


Fig. 1.—Temperature curve in Case 3.

abscess; it was considered necessary to have recourse eventually to surgical intervention. However, in consideration of the grave condition of the patient and her decided refusal of such a proceeding, the operation was put off for a time.

The temperature, always at a high level, showed decided daily oscillations, with a tendency from time to time to fall gradually, but shortly returning to the same level. It was more than 39 in the evening, and 37 and 36.8 in the morning. The pulse, however, slackened from 120 to 100 a minute. The jaundice began slowly to disappear; the peritoneal symptoms passed; all the subjective complaints ceased, and the general condition of the patient, which until then had been almost hopeless, seemed to change for the better. On the other hand, diarrhea appeared; the spleen, which at the beginning was not palpable, became considerably enlarged, its lower edge reaching the horizontal navel line. The number of white cells in the blood decreased to 6,400 per cubic millimeter, whereas there were 19,000 in the beginning. The differential count revealed 75 per cent. of neutrophils; there were 90 per cent. before.

In the sacral region, in the region of both the greater trochanters, and in other places (for instance, on both sides of the chest) large and deep bedsores, which were now the real and principal cause of ailment, began to form. The general cachexia of the patient then reached a high grade. The result of hemoculture, two weeks after the first, was negative. The Widal reaction, however, positive before in the dilution of 1:50, rose to 1:400. (We must note especially that in many cases of cholelithiasis, with or devoid of jaundice, and with typhus abdominalis many years before, the Widal reaction in the serum always was negative.)

This condition lasted about three months. The morning and the evening temperatures always showed great differences but gradually commenced to fall. The bedsores, which were deep and putrid, began to heal nicely; the jaundice had long disappeared, leaving no traces. The pulse was fairly strong, in general not surpassing 100 beats a minute, but the cachexia was great and the patient died.

The macroscopic postmortem examination revealed that there were no affections of the mucous membrane of the intestine. The capsula of the liver, however, showed a considerable thickening and adhesions to the surrounding organs, the colon transversalis, the stomach and the diaphragm. The pylorus region was adherent to the lower surface of the liver. The gallbladder was small, shrunken and closely packed with stones. The hepatic, cystic and choledochus ducts were of a little fingerbreadth and filled with a quantity of stones, each the size of a medium sized bean and of irregular form. The liver, on being laid open, was completely covered with grayish green spots, from the size of a pinhead to that of a pea. In the center of each spot was the small aperture of a gall duct, besides many small cavities filled with pus, ranging in size from that of a small pea to that of a bean. In the right lobe, there was hardly any healthy tissue; in the left, the changes were not so extensive but were considerable. The diagnosis was cholangeitis, pericholangitis purulenta and multiple hepatic abscess. The affections of the kidneys and of the heart corresponded to a chronic septic process.

Two factors contributed toward the peculiar infection in this case: (1) the previous typhoid, after which the microbes remained somewhere in the organism, probably in the gall canals, in order that at a proper moment, overcoming all resistance, they might get into the blood and attack the organism; (2) an old gallbladder disease, which formed in the liver—the place most disposed to catch infection—a locus minoris resistentiae.

In our fourth case we had generally a similar course of events but in lighter form.

Case 4.—A woman, aged 43, complained of a jaundice and sharp pain in the region of the liver, radiating toward the right shoulder-blade and the lower ribs, the pain being of three days' duration. The patient had this pain with vomiting for the first time three months before; the vomiting was followed by jaundice. She was under a physician's care for five weeks, after which she felt quite well until her present illness. She had never been ill before; she had five normal deliveries and afterward four pregnancies that terminated before the third month.

The physical examination showed: a distinct yellowish tinge of the skin and the sclerae; a slight dulness over the right collar-bone and in the back; a weakness of the breath sounds over the lower part of the right lung; the second sounds at the base of the heart fairly strong, the second aortic sound, accentuated; the abdomen distended, especially in its lower part; a distinct muscular resistance (defense musculaire) in the right half of the abdomen, most considerable in the upper quadrant; pain in the abdomen on pressure which was slighter on the removal of pressure; the spleen not palpable; palpation of the liver impossible on account of the distended state of the abdomen; the tendinous reflexes present; temperature, 39 C.; pulse, 128, and respiration, 28.

Examination of the urine revealed: specific gravity, 1.024; albumin, 0.4 per thousand; a trace of urobilinogen; a doubtful trace of the bile pigments. Hay's test was positive; the diazoreaction was negative. In the sediment there were a few cells and from one to two granular casts in the microscope field. Hemoglobin totaled 98 per cent.; red cells, 4,300,000; white cells, 14,800. The differential count was: polymorphonuclear neutrophils, 72 per cent.; lymphocytes, 26 per cent.; platelets, 150,000. The bleeding time was two minutes; the coagulation time, six

minutes. By the van den Bergh test the bilirubin in the serum was about 3 units; the direct test was positive after one minute. The Wassermann reaction in the serum was negative; the result of the hemoculture was negative. In the feces the Schmidt test was positive; blood was not found, and on inspection under the microscope no white cells were discovered.

During the next four or five days, the temperature became subfebrile; the abdominal symptoms passed almost completely; the liver was now palpable three fingerbreadths under the edge of the rib, hard, smooth and sore; the jaundice passed; the albumin, bile acids and granular casts disappeared, leaving no trace. The diazoreaction remained negative. On the other hand, a dulness with an almost complete absence of breath sounds appeared over the lower part of the right lung and over the region of the right angle of the shoulder, egophony and bruit de souffle.

The condition of the patient, after a passing improvement, became considerably worse; the temperature rose and disturbing pain appeared in the right side. Exploratory punctures of the right pleura, repeated twice, each gave 3 c.c. of a turbid liquid, with a considerable amount of fibrin and 5 per cent. of albumin. The differential count of the liquid sediment was as follows: 75 per cent. neutrophils, 23 per cent. lymphocytes and 14 per cent endothelial cells.

During the patient's first week in the hospital, diarrhea changed to constipation. The process continued in this way for about two weeks, during which numerous râles of a fine character appeared on the right axillary line, with tubular breath sounds in the region of the fourth and fifth ribs (on the same line). A dulness, beginning from the angle of the shoulder-blade posteriorly and from the upper edge of the fourth rib in the front, still continued. The temperature was intermittent. The patient felt generally bad. Under the arch of the ribs, the edge of the spleen became palpable. The sacrum and the feet became swollen. A second exploratory puncture of the pleura gave a negative result. A renewed blood examination showed: 9,600 white cells; neutrophils, 74 per cent.; lymphocytes, 23 per cent.; monocytes and transitionals, 3 per cent. Bilirubin in the serum totaled 0.8 units. Nothing particular was noted in the urine. The continued fever, the simultaneous occupation of the liver and the lungs by the affecting factor and the swelling of the spleen suggested the typhoid infection and the Widal reaction in the serum, which was positive in a dilution of 1:400 with typhoid bacilli (negative with paratyphoid A and B bacilli), confirmed our supposition that we had to do with a typhoid infection. The further course of this case did not give any particular result. During the fourth week, the temperature began to be nearly normal, the pulse from 100 and 96 slackened down to 84; the pulmonary symptoms passed little by little, and the patient, after a two month stay in the hospital, was discharged as healthy.

A year and a half before this article was written, we observed a fifth case, quite analogous to the foregoing two, which we shall mention only, and which as regards graveness, ranked between these two cases.

Case 5.—A woman complained of symptoms of cholecystitis and cholangeitis purulenta, with a distinct jaundice, high temperature and considerable leukocytosis with neutrophilia. Typhoid fever existed in the history of the illness. In the further course an inflammation of both lungs appeared, with extreme cachexia and bedsores. After only four or five weeks, when the temperature began to fall and the patient to recover, the characteristic appearance of the temperature curve on the chart, suggested typhoid infection. (It was our first case of that type.) The Widal reaction in the serum was decidedly positive even in the dilution of 1:800, and the hemoculture was negative.

The further favorable course of the illness, in spite of the critical condition of the patient, the speedy healing of the bedsores, the amazingly quick return of strength, and the general recovery left no doubt as to the typhoid nature of this case.

In all these cases, except Case 2, the typhoid infection took the form of an acute illness of the liver and bile ducts, with jaundice, leukocytosis and neutrophilia, although in its further course, we observed symptoms of typhus abdominalis, diarrhea, swelling of the spleen, etc. On post-mortem examination in Case 3, none of the characteristic changes of typhoid fever were seen, especially no affections of the mucous membrane of the intestine. Also jaundice during typhus abdominalis is a rarity. In the 300 such cases that passed through our hands in the time of the epidemic of 1922, jaundice appeared in only one case, during a fairly grave relapse of the sickness. Jürgens,[1] for instance, when discussing several variations and peculiarities in the course of typhoid, accentuates the fact that "jaundice is a great rarity, even a very slight yellowish tinge being such an unusual phenomenon that the presence of this symptom speaks against the diagnosis of typhus abdominalis." As a fact of particular interest, we may mention that in our cases, in spite of the process being caused by the typhoid bacillus, and this bacillus being received in a pure culture from the blood (Case 3), we met with a high leukocytosis with neutrophilia, as in every acute infectious process. It is therefore obvious that the characteristic feature of typhoid fever, leukopenia with neutropenia, does not depend on some special qualities of the Eberth bacillus itself nor on its presence in the blood, but is due to its localization in the lymphatic system.

In case of a different localization of this bacillus, the organism reacts on the typhoid infection not with leukopenia but with leukocytosis.

The observation of Naegeli agrees with our supposition. He says that during the first two days of typhus abdominalis the number of white cells in the blood increases at the cost of neutrophils and that the neutropenia appears only afterward. Probably at the beginning of typhus abdominalis we have to do exclusively with a general infection without a special localization in the lymphatic system of the alimentary tract. During this period of typhus abdominalis just as in our cases, the organism reacts, on the invasion of the Eberth bacilli, with leukocytosis and neutrophilia.

To our knowledge there are in the medical literature few cases similar to the one mentioned in the foregoing. In 1901 Besançon [2] published a case of the cholecystitis catarrhalis with the temperature resembling typhoid but without the period of continuation and without the clinical symptoms of typhus abdominalis, the Widal reaction being positive in a dilution of 1 : 600.

---

1. Jürgens, S.: Spezielle Pathologie und Therapie inner Krankheiten. Kraus und Bruggsch **2**.

2. Besancon, M. F.: Semaine méd., 1901, p. 396.

Based on these grounds, the author states that the Eberth bacillus can behave like a simple saprophytic microbe and evoke quite a common illness, analogous with our first case.

Leignel-Lavartine [3] describe an acute inflammation of the gallbladder and of the surrounding tissues during typhus abdominalis.

Abrami and Gautier [4] noticed a case of obstructive jaundice with complete retention of the bile pigments, but without the retention of the bile acids (a completely dissociated jaundice) in the course of typhus abdominalis. Postmortem examination revealed the exclusive disease of the parenchymatous tissue of the liver, hepatitis diffusa, without the slightest affection of the larger and the smaller gall ducts.

Guinon and Gendrou [5] give an interesting case bearing great resemblance to our Case 3, the patient, being a child, aged 5 years. A few days after its father's death from typhus abdominalis, temperature appeared; after ten days, the obstructive jaundice with splenomegalia; on the twenty-seventh day, the jaundice subsided and the classic picture of typhoid fever developed, with roseola, involvement of the lungs, etc.

In 1911 Janowsky [6] also published a case of a grave typhus abdominalis, in which after three weeks general indisposition with temperature the jaundice appeared together with vomiting. The author, who at this period was called to the patient for the first time, found a considerable enlargement of the liver and the spleen, the abdomen distended and painfulness in the right iliac region. He diagnosed typhus abdominalis. The diagnosis was afterward confirmed by the positive result of the Widal reaction in the serum, 1 : 120, and by an almost imperceptible intestinal bleeding in the further course. This case, considered by the author as a rare form of typhus abdominalis, is similar to the mentioned case of Guignon and Gendron; it differs, however, from our last three cases in that the jaundice appeared after a three weeks illness, while in our cases the affection of the liver appeared at the beginning, a fact that makes our cases still more interesting.

The peculiarity of our cases that should be especially accentuated is that the typhoid infection passed without the implication of the intestinal lymphatic system.

As corresponding to the foregoing cases, especially Case 3, we mention the last case under our observation, a liver abscess, caused, it is true, not by the typhoid but by the paratyphoid A bacillus, on the

3. Leignel-Lavartine: Séance de la Soc. Méd. d. Hopitaux, Feb. 14 and Feb. 21, 1909; Semaine méd., 1909, p. 249.

4. Abrami and Gautier: Séance de la Soc. Méd. d. Hopitaux, Dec. 13, 1912; Semaine méd., 1912, p. 610.

5. Guinon and Gendron: Séance de la Soc. Méd. d. Hopitaux, Dec. 16, 1910; Semaine méd., 1910, p. 607.

6. Janowsky, W.: Gaz. lek., 1911, p. 19.

grounds of an old and chronic inflammation of the gallbladder and the surrounding tissues.

CASE 6.—A woman, aged 60, complained of pain in the region of the right rib arch, with shivering, vomiting and, according to her statement, feverishness. When she was questioned further, it appeared that for the last ten years she had suffered from similar attacks of pain, which occurred seldom in the beginning, once or twice in a year, but lately every two or three months, especially in the night; they lasted a few hours and were never accompanied by jaundice. At the age of 14, she was supposed to have had typhoid fever. On physical examination, nothing particular was found, except a slight accentuation of the second pulmonary sound and a slight painfulness under the right rib arch. In the catheter specimen of the urine, except an occasional white cell in the microscopic field, nothing particular was noted. The temperature during the first four days of her stay in the hospital was normal. On the fifth day it began to rise in a fairly irregular way to 40 C., and after staying at this level from twenty-four to forty-eight hours fell to 38 and 36.

In the meantime, the condition of the patient became as bad as was possible. A state of complete numbness speedily ensued; there were however, no subjec-

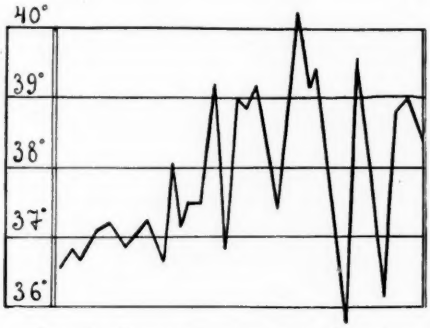


Fig. 2.—Temperature curve in Case 6.

tive complaints and no possibility of determining any affections, except a slight sensitiveness under the right rib arch and a slightly marked Murphy's sign. Nevertheless, the bad pulse (always more than 100), the constant numbness, the raspberry colored, dry tongue, the dry throat and the diarrhea (from three to four liquid stools in twenty-four hours), all gave the picture of a grave illness, with the diagnosis oscillating between typhus abdominalis and tuberculosis miliaris acuta.

At the beginning of the fever state, the blood count revealed 5,400 white cells per cubic millimeter. The differential count was: neutrophils, 58 per cent.; lymphocytes, 38 per cent., and transitionals, 4 per cent. After seven days the repeated examination revealed 11,800 white cells per cubic millimeter, the differential count being neutrophils, 85 per cent., and lymphocytes 12 per cent. The bilirubin in the serum was 0.7 units, van den Bergh; cholesterin, 0.28 per thousand. The Wasserman reaction was negative. The hemoculture on sugar, boullion and bile was negative.

The Widal test in the serum, performed on the fifth day after the patient's temperature first rose on the ninth day of her stay in the hospital, was negative with the typhoid and the paratyphoid B bacillus, and positive with the paratyphoid A bacillus in the dilution of 1:400; five days later, the repeated test was again positive only with paratyphoid bacillus in a dilution of 1:100.

The examination of the urine showed: albuminuria 0.2 per thousand, red cells, and endothelial cells from the upper urinary tract. The diazoreaction remained negative. Gall acids and gall pigments were absent. No remarkable abdominal symptoms were present.

On the sixteenth day of her stay in the hospital and twelve days after her temperature first rose, the patient died.

The postmortem examination revealed the following conditions: The gallbladder was small, shrunken and quite hidden in adhesions, with the surrounding tissues and the lower liver surface. No stones were present. An abscess was found boring into the depth of the right liver lobe and reaching the region of the gallbladder neck. There were glomerulonephritis, enlargement of the spleen, and septic tumor, a degeneration of the parenchymatous organs, the liver and the heart muscle. This case is unusually interesting: (1) as an example of the possibility that the gallbladder may be inflamed for many years without the formation of stones; (2) as an evident liver abscess that arose on the grounds of the infection with paratyphoid A bacillus, whose presence was not disclosed by any remarkable clinical symptom.

It is difficult to judge in Case 6 if we had to do with a sudden augmentation of the virulence of the paratyphoid A bacilli in the organism, which for a long time had been their carrier and in which they caused a chronic inflammation of the gallbladder, or if it was a fresh invasion of the gallbladder by the paratyphoid A bacilli, the gallbladder being free from typhoid infection though affected by a former illness.

The only way to clear up this doubt would be to make the Widal test in the serum during the period preceding the pyretic state. The positive result of this test would indicate that we had to do with a constant carrier of the micro-organisms; the negative, in addition to the later results, would favor a fresh and independent infection.

CONCLUSIONS

1. The existence of typhoid bacteriemia and a positive Widal reaction in high dilution, 1 : 400, 1 : 800, along with a high temperature is not always an absolute proof of typhus abdominalis.

2. The mentioned conditions may be observed in states of typhoid infection, located most often in the liver and the gallbladder.

3. Such states of typhoid infection, although in some sense similar to typhoid fever, differ from the latter in (*a*) the presence of leukocytosis with neutrophilia; (*b*) the absence of roseola, and (*c*) the absence of the changes in the lymphatic system of the alimentary tract.

4. The leukopenia with neutropenia, one of the most characteristic symptoms of typhus abdominalis, probably does not depend on the biologic quality of the typhoid bacillus but on its secondary seat in the lymphatic system of the alimentary tract.

THE EFFECT OF HEART MUSCLE DISEASE ON THE ELECTROCARDIOGRAM *

ARTHUR W. MASTER, M.D.

AND

HAROLD E. B. PARDEE, M.D.

NEW YORK

Pathologists and clinicians have long been engaged in the correlation of the symptoms and signs of heart failure with the condition of the heart as found at necropsy. With the advent of the electrocardiograph, investigators promptly began to make comparisons between the normal and abnormal function of the heart and the electrical current produced by that organ. This correlation has led to a quite thorough understanding of the mechanism of cardiac arrhythmia.

The correlation of structural disease of the heart with abnormalities of the electrocardiogram has proceeded more slowly, and it has been our purpose to report in detail a series of cases in which the gross and microscopic appearance of the ventricular muscle is compared with the ventricular complexes of the electrocardiogram. We are endeavoring to decide whether an abnormal ventricular complex must mean myocardial disease and whether a normal ventricular complex will be produced by only a normal muscle. We are able from this study to throw some light on the relation between certain abnormalities of the ventricular waves of the electrocardiogram and the type of pathologic change within the heart muscle.

Previous work has been especially concerned with the association of particular abnormalities of the waves with particular pathologic changes. It is our aim to attack the more general problem of the relation between the electrocardiogram and heart muscle disease.

The electrocardiogram of the normal heart beat consists of the P wave, due to auricular activity, and the Q-R-S group and the T wave, which are the result of ventricular action. There are certain features of these waves which have been found to occur in records from normal hearts and others which have been found only in records from hearts suspected of being abnormal.[1]

---

* From the Medical and Pathological Departments of Cornell University Medical College.

1. Pardee, H. E. B., and Master, A. M.: Electrocardiograms and Heart Muscle Disease, J. A. M. A. **80**:99 (Jan. 13) 1923. Pardee, H. E. B.: The Clinical Aspects of the Electrocardiogram, New York, Paul B. Hoeber, 1924.

Einthoven's signs of hypertrophy of the right or left ventricle [2] are now considered to indicate the direction of the predominant electrical effect of the Q-R-S group rather than solely a muscular hypertrophy.[3] These changes do not indicate pathologic muscle, though they may indicate one that is hypertrophied.

Notching of the Q-R-S group is an abnormal feature if found near the peak of a wave in the lead giving that wave a relatively large excursion. It will, under these circumstances, be associated with a notching or slurring of the Q-R-S group in one or both of the other leads. Prolonged duration of the Q-R-S group is abnormal if the prolongation exceeds 0.1 second, but in a heart that is much enlarged or that gives a record of marked left predominance 0.12 second may be considered normal.

A voltage of the Q-R-S group so low that its size does not exceed 5 mm. in the lead of largest excursion is a significant abnormal finding. If the T wave is turned downward in Lead I or Lead II, or both, it is an abnormal feature. Moreover, there is a special form to the T wave which is believed to be characteristic of coronary artery occlusion with an area of deficient blood supply in the ventricular muscle. The wave shows an upward convexity followed by a sharp downward peak in one lead. If this occurs in Lead III alone it is not significant unless T_2 is turned downward, although T_2 need not show the peculiar upward convexity.

Certain combinations of these abnormalities tend to occur together frequently. Perhaps the most common combination is the "arborization block" of Oppenheimer and Rothschild [4] in which a prolongation of the Q-R-S complex beyond 0.1 second, notching of the R wave and low voltage occur.

Another common form of abnormal curve is considered to indicate bundle branch block. In this case a notched Q-R-S group occurs with a lengthening of the duration to 0.14 second or more. The chief deflection here is either upward in Lead I and downward in Lead III or vice versa. The Q-R-S group turns smoothly into the T wave, which is directed opposite to the chief deflection of the Q-R-S group.

Our studies are concerned with eleven hearts obtained at the New York Hospital from patients who died of heart failure. They were from the medical services of Drs. L. A. Conner and W. R. Williams. The hearts were turned over to us for microscopic examination and we

---

2. Einthoven, W.: Weiteres über Elektrokardiogram, Arch. f. d. ges. Physiol. **122**:517, 1908.

3. Lewis, T.: Observations on Ventricular Hypertrophy, with Especial Reference to Preponderance of One or Another Chamber, Heart **5**:367, 1913-1914.

4. Oppenheimer, B. S., and Rothschild, M. A.: Electrocardiographic Changes Associated with Myocardial Involvement, J. A. M. A. **69**:429 (Aug. 11) 1917.

noted the gross and detailed findings. Sections were taken from the lateral wall of each ventricle, from the interventricular septum in its middle portion and from the right auricular muscle. These were stained with the ordinary hemotoxylin eosin and with Herxheimer's scharlach r as described by Mallory and Wright.[5]

As controls, similar sections from thirteen normal hearts were obtained at the Bellevue Morgue (New York City) through the courtesy of Dr. Douglas Symmers. These hearts were from persons who averaged about 30 years of age and had met a sudden death, e. g., by bullet, stab wound or fall, and whose vicera were apparently free from disease. The same stains were used in this series as in the pathologic hearts.

It was only after thorough study of slides from similar portions of the hearts of the control series that we felt able to decide what should be called normal heart muscle. We found particularly that the picture which most pathologists would call fatty degeneration was often present in the normal hearts of our control series.[6] In other words, we found that cardiac muscle normally contains a considerable amount of microscopically demonstrable fat; so we were not so ready to report fatty degeneration of the fibers as we might otherwise have been.

We also were able to gage more accurately how much connective tissue should be found between the muscle cells and the bundles and how much round cell infiltration could be considered normal.

We feel quite certain that many authors have reported fatty degeneration of the heart when this condition was not present. Had it not been for the controls we should certainly have wrongly considered that some of our pathologic hearts showed fatty degeneration or diffuse round cell infiltration or both.

In our present series we have considered the slightest departure from normal to be an increase of the cells of the interstitial fibrous tissue (Fig. 9). As this progresses it leads to what has been called fibrous tissue replacement, the microscope showing more or less dense bands of fibrous tissue between or within the muscle bundles (Fig. 14). When this is extreme it leads to a change in the macroscopic appearance of the muscle. This picture may possibly come about at times through a primary degeneration of muscle fibers with secondary fibrous replacement. We also noted patches of fibrous replacement with relatively little muscle tissue, which had resulted from old infarcted areas.

We do not feel persuaded that such apparent changes as thinning or thickening of the individual muscle fibers, fragmentation, cloudy degeneration or even fatty degeneration, as it is usually diagnosed from the

5. Mallory and Wright: Histological Technique, Ed. 7, p. 167.

6. Master, A. M.: Fatty Degeneration of the Heart, Arch. Int. Med. **31**:221 (Feb.) 1923.

Clinical Diagnosis, Electrocardiogram and Pathologic Findings in Cases Studied

Case	Diagnosis	Electrocardiogram Ventricular Waves	Heart	Coronary Arteries	Microscopic Examination
1	Chronic interstitial nephritis; chronic arteriosclerosis	Borderline r. v. p.; downward T wave in all leads (digitalis)	Enlarged, 600 gm.	Slight coronary atheroma.....	Muscle normal
2	Aortic stenosis and regurgitation; mitral stenosis; auricular fibrillation; tertiary syphilis	Borderlin l. v. p.; downward T wave in all leads (digitalis)	Enlarged, 540 gm.	Markedly thickened and calcified, no narrowing or occlusion	Muscle normal except for slight fibrous replacement in left portion of interventricular septum
3	Rheumatic mitral stenosis and regurgitation; heart block	Slight l. v. p.	Large, 425 gm.	Moderate atheroma, no narrowing	Muscle practically normal; possibly a slight increase in fibrous tissue
4	Rheumatic aortic regurgitation; mitral regurgitation and stenosis; acute pericarditis with adhesions	Normal except Q-R-S = 0.12 second	Greatly enlarged, pericardium adherent in many places	Normal	Muscle normal except for slight invasion of the inflammatory process from pericardium
5	Coronary thrombosis; chronic arteriosclerosis	R. v. p.; T wave downward in Leads II and III and in Lead III, with an upward convexity before the downward peak	Large, 500 gm.; large pale focus on posterior surface of left ventricle where fibrous replacement was the predominant feature in section	Thickened lumen of anterior descending branch occluded by thrombosis at its first main division	On posterior surface of left ventricle and in lower part of the septum, especially on the left side, areas of necrosis of the muscle with the usual accompanying inflammatory reaction; muscle of right vent ... normal except for slight increase of interstitial tissue
6	Chronic arteriosclerosis; coronary artery disease; chronic myocarditis	Borderline l. v. p.; small Q-R-S excursions; R = 6 mm.; downward T wave in Leads I and II	Much enlarged, 875 gm.; endocardium appeared normal; wall of left ventricle thinned and had scattered gray areas	Diseases and had calcareous deposits; left artery especially involved and for 3 cm. almost obliterated	Marked increase of interstitial fibrous tissue and some fibrous replacement; right ventricle had only increase of interstitial tissue
7	Chronic arteriosclerosis; chronic myocarditis	All waves very small; downward T wave in Leads I and II	Much enlarged, surface fat abnormally widespread and thick and left ventricle muscle somewhat thinned	Markedly thickened and calcified and narrowed throughout, but no occlusion	Considerable fibrous tissue replacement in left ventricle, and in septum no replacement, but moderate increase of interstitial fibrous tissue
8	Chronic arteriosclerosis; chronic myocarditis; auricular fibrillation	Marked l. v. p.; Q-R-S group notched; downward T wave in Lead I	Markedly enlarged, 640 gm.; left ventricle had numerous small areas of fibrosis, and at apex a thinned, fibrous, partly calcified area; patchy sclerosis of the endocardium, especially at apical part of left side of septum	Marked atheroma with narrowing, especially in anterior descending branch of left coronary, which was almost obliterated	Muscle had marked increase of interstitial fibrous tissue; no fibrous replacement except in area at apex of left ventricle; right ventricle had only slight change
9	Chronic arteriosclerosis; chronic interstitial nephritis; gangrene of lung; bronchopneumonia	Marked l. v. p.; Q-R-S group notched; downward T wave, Leads I and II	Much enlarged, 740 gm.; endocardium of both ventricles thickened, especially on septal surface of left ventricle	Extensive atheromatous plaques; little thickening; no occlusion	Muscle showed diffuse but only slight increase of interstitial fibrous tissue; septal endocardium of left ventricle much thickened
10	Chronic arteriosclerosis; chronic interstitial nephritis; aortitis; auricular fibrillation	Wide Q-R-S group; notched Q-R-S group; curve suggests partial lesion of right branch auriculoventricular bundle	Much enlarged, 575 gm.; left ventricle thinned toward apex; endocardium of right ventricle thickened in region between anterior and posterior papillary muscles	Stiffened and tortuous; no occlusion	Muscle in left ventricle had numerous dense patches of fibrous tissue replacement, elsewhere a moderate to marked increase of the interstitial fibrous tissue
11	Rheumatic mitral stenosis; mitral regurgitation	Small waves; wide Q-R-S group; notched Q-R-S group; downward T wave in Leads II and III	Large, 475 gm.; muscle and endocardium appeared normal except for diseased mitral valve	Little or not at all thickened; slight atheroma; no narrowing	Muscle had considerable fibrous tissue replacement, especially marked in the left ventricle but not accentuated in subendocardial muscle layers

presence of fat droplets within the muscle fibers, actually mean anything more than a varying technic of staining or fixing or cutting of the sections.

The case histories, electrocardiographic and pathologic findings which follow are briefly summarized in the accompanying table.

REPORT OF CASES

CASE 1.—A man, aged 51, was admitted four times to New York Hospital. In 1911 he entered the institution for chronic lead poisoning and pyorrhea alveolaris and in 1913 he had an abscess of the lung. Dec. 1, 1920, he was admitted for bronchial asthma, but features of chronic interstitial nephritis, arteriosclerosis

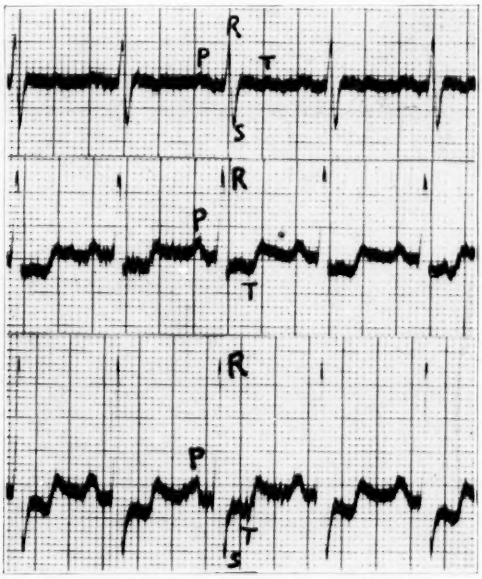


Fig. 1 (Case 1).—Q-R-S group, showing right predominance; the T waves are downward in Leads I and II.

and chronic lead poisoning were present. He was discharged Jan. 9, 1921. The patient was admitted for the last time January 21, and died February 7. He was orthopneic and weak and suffered severely from attacks of paroxysmal dyspnea. His lungs contained many râles suggesting bronchial asthma. In December, 1920, his heart was enlarged 2 cm. to the right and 13 cm. to the left of the midsternal line in the fifth space, and a soft systolic murmur was heard at the apex. At the end of January, 1921, the dulness of the heart had increased to 16 cm. to the left in the sixth space and 3 to the right in the third space. A gallop rhythm was present. Sounds at the apex were muffled. The radial vessels were sclerotic. The liver palpated 4 cm. below the costal margin.

The blood pressure ranged between 190 and 210 systolic, and 90 and 110 diastolic. The urine had a specific gravity of 1.012-1.015, with albumin and granular and epithelial casts. The urea nitrogen was 64-71 mg. and creatinin 4.2-4.6 mg.

The electrocardiogram three days previous to death (Fig. 1) showed a Q-R-S group on the borderline of right ventricular predominance. The T wave was sharply downward in Leads II and III, and slightly so in Lead I; but the patient had received about 700 minims of the tincture of digitalis during the previous thirteen days.

The necropsy diagnosis was: chronic interstitial nephritis; hypertrophy of the heart; edema of the lungs; chronic fibrinous pleurisy; arteriosclerosis of the aorta, and fibroma of the kidney.

Gross examination of the heart showed that it was much enlarged, weighing 600 gm., and that the walls of both ventricles were thickened. The valves and muscle appeared normal. The coronaries showed a few small, roughened areas in the intima. The aorta showed very slight arteriosclerosis with a few scattered noncalcified plaques.

Microscopic examination of the heart muscle revealed no abnormality and no fatty degeneration.

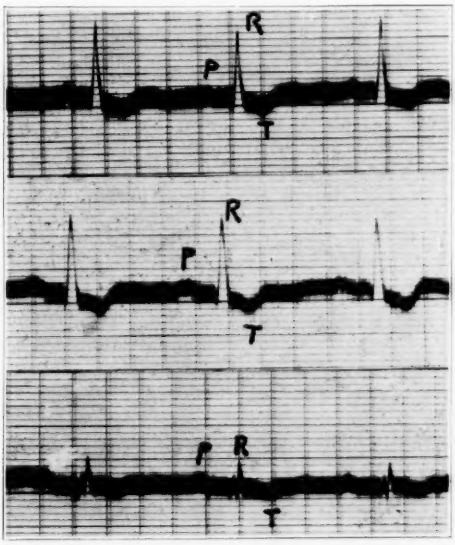


Fig. 2 (Case 2).—Normal Q-R-S group; the downward T waves of Leads I and II probably are a digitalis effect.

CASE 2.—A man, aged 65, who was admitted Nov. 11, 1916, and died December 22, had complained of shortness of breath, especially on exertion, and of palpitation, cough, and swelling of ankles from May onward. He was dyspneic and orthopneic on examination, and diffuse, squeaky râles were present in the chest. The heart was not enlarged, but the action was completely irregular, suggesting auricular fibrillation. There was a loud systolic murmur at the apex and a blowing diastolic murmur over the base and body of the heart, as well as a rough systolic murmur and a systolic thrill at the aortic area. The liver was palpable. The blood pressure ranged between 150 and 180 systolic and was 50 diastolic. The urine showed a faint trace of albumin, with granular casts; the nonprotein nitrogen was 69 mg. Before death the patient complained of pain in the right leg.

The electrocardiogram five days before death (Fig. 2) showed a prolonged auriculoventricular conduction time, 0.24 second. The Q-R-S group was on the

border of left ventricular predominance. The T wave was downward in all three leads, which may be explained by the patient's marked digitalization. (November 10-12, 150 minims of the tincture, November 12-16, 240 minims, and November 16-December 11, 30 minims were given twice a day.)

At necropsy the diagnosis was: chronic valvular disease; hypertrophy of the heart; chronic nephritis; general arteriosclerosis; hydrothorax; chronic pleurisy, and thrombosis of the right tibial artery.

The gross examination of the heart showed an organ considerably enlarged, weighing 540 gm. Both mitral and aortic valves were thickened and calcified, and the orifices, especially the aortic, were stenosed. The muscle appeared normal. The coronaries were markedly thickened and calcified. There was moderate narrowing but no occlusion. The aorta showed numerous areas of atheroma especially in the abdominal portion.

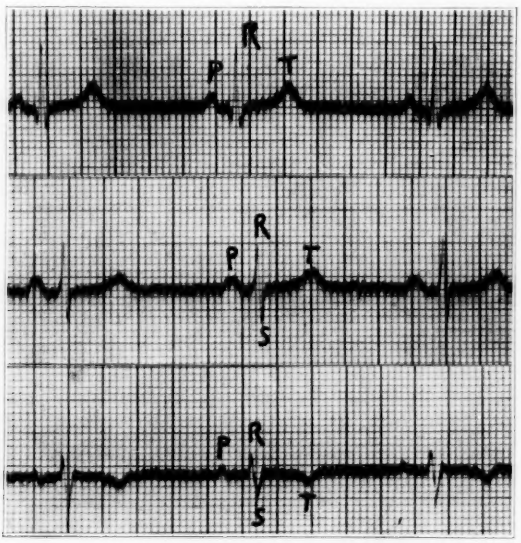


Fig. 3 (Case 3).—Normal record except for slight left predominance of the Q-R-S group.

Microscopic examination revealed no abnormality of the ventricular muscle except for an area in the left portion of the interventricular septum where there was a slight degree of fibrous tissue replacement. No fatty degeneration was found.

Case 3.—A man, aged 52, gave a history of spells of weakness, palpitation and fainting from December, 1919, to April, 1920. These attacks were typical of Stokes-Adams' disease. There was an interval of freedom from attacks for one month. However, these recurred in June and the patient died July 3, 1920.

During life the heart was only slightly enlarged, and presented a complete heart block with the auricles beating at the rate of 100 and the ventricles at 27, except during the one month period of freedom, when the conduction time was normal. A soft blowing systolic murmur was heard at the apex. The blood pressure ranged between 140 and 180 systolic, and 70 and 100 diastolic. The urine showed a faint trace of albumin; the nonprotein nitrogen was 38 mg. The Wassermann reaction was negative.

The electrocardiogram taken 11 days previous to death (Fig. 3) showed a ventricular complex with a slight left predominance but with no other abnormality.

The necropsy diagnosis was: chronic myocarditis; chronic cardiovalvular disease; chronic interstitial nephritis; right hydrothorax; cirrhosis of the liver; general arteriosclerosis, and edema of the lungs.

The gross examination of the heart showed that it was moderately enlarged, weighing 425 gm. The mitral valve was thickened and contracted; the left auriculoventricular ring was calcified for about three fourths of its circumference. The left ventricle was hypertrophied; the muscle appeared to have some increase in fibrous tissue but had no focal lesions. The left auricular wall was thickened

Fig. 4 (Case 3).—Practically normal muscle, with little if any increase of interstitial connective tissue; at the top, a blood vessel cut longitudinally.

as was the endocardium of this chamber. The coronaries showed moderate atheroma but no narrowing. The aorta was moderately atheromatous.

The microscopic examination revealed a practically normal muscle with very little if any increase of interstitial connective tissue (Fig. 4). There was no fatty degeneration.

Case 4.—A man, aged 22, whose first admission dated from June 4 to July 19, 1920, was admitted for the second time July 26 and died Feb. 7, 1921. At the first admission he complained of abdominal cramps; he was operated on but no diseased condition was found. After this operation, he complained of shortness of breath, palpitation, cough and finally swollen legs. The heart percussed

15 cm. to the left of the midsternal line in the sixth space, 7 cm. to the right in the fourth space. A systolic thrill and a diffuse impulse were present over the entire precordium. The patient showed the murmurs of aortic regurgitation and of mitral regurgitation and stenosis. The liver was palpated to the level of the umbilicus. The patient developed fluid in the pericardial sac. The blood pressure was 130 systolic, 75 diastolic. The specific gravity of the urine was from 1.022 to 1.033; there was a very faint trace of albumin, and granular casts were present at times.

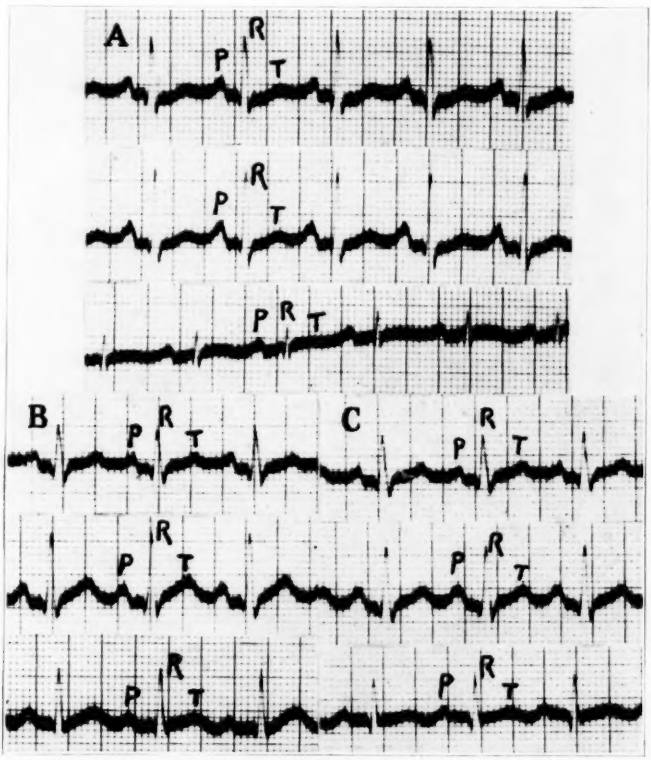


Fig. 5 (Case 4).—*A*, record of January 25, showing a Q-R-S duration of 0.1 second; *B*, record of February 5 before the pericardial tapping, with a Q-R-S duration of 0.12 second; *C*, record of February 5 after the tapping.

The electrocardiogram, Figure 5 *B* and *C*, taken two days before death, showed no abnormality (but see text) except a Q-R-S duration of 0.12 second. There was no ventricular predominance.

The necropsy diagnosis was: chronic myocarditis; chronic vegetative endocarditis (all valves); chronic fibrinous pericarditis (adherent pericarditis); infarcts of the lung, the spleen and the left kidney, and chronic passive congestion of the viscera.

The gross examination of the heart showed a marked fibrous pericarditis with soft but firm adhesions and some fluid. The heart was greatly enlarged, both

ventricles being thickened. All valves showed small, fresh vegetations. The mitral valve was stenosed. The aortic valve segments were thickened. No gross area of fibrosis was observed in the heart muscle.

The microscopic examination revealed a slight diffuse round cell infiltration in the subpericardial layers of the muscle of both ventricles, apparently an extension of the pericarditis; elsewhere there was no increase of fibrous tissue, and there was no fatty degeneration.

CASE 5.—A man, aged 59, was admitted to New York Hospital May 25, 1921, and died June 7. Sixteen months before entering the hospital he had a severe attack of abdominal gas pains. This was followed by recurrences of increasing frequency, with belching and dyspnea on exertion. A cough was present, June 3. The pulse became irregular, and the heart was slightly enlarged, the sounds being distant. The blood pressure was 100 systolic, and 70 diastolic; the urine was normal, and the Wassermann reaction was negative. Clinically,

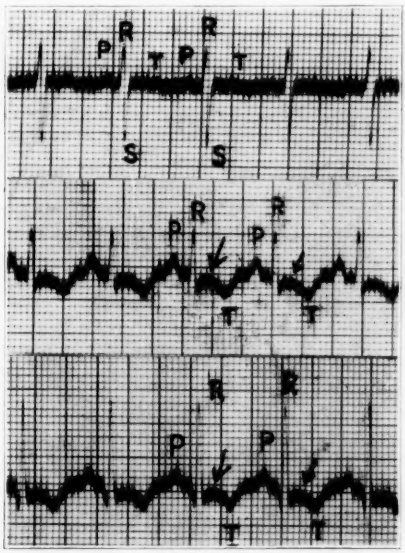


Fig. 6 (Case 5).—Q-R-S group, showing right predominance; the T wave is downward in Lead II and has the upward convexity of the R-T interval due to localized coronary narrowing.

the patient was considered to have coronary artery disease with thrombosis of a branch.

The electrocardiogram taken thirteen days before death (Fig. 6) showed a right ventricular predominance. The T wave was downward in all three leads, and the upward convexity which preceded T in Leads II and III was like that which has been associated with coronary artery occlusion.

The gross examination of the heart revealed an enlarged, soft, flabby organ, weighing 500 gm. The left ventricle was distinctly dilated and on its posterior surface near the apex was a definite, infarcted area about 9 sq. cm. in size. The muscle was thinned and pale in this region; on the corresponding endocardial surface it was grayish yellow. The adjacent portion of the septum was similarly involved. The coronaries showed marked thickening. The lumen of the anterior descending branch of the left coronary was occluded by an old thrombus.

Microscopic examination revealed muscle necrosis and fatty degeneration in the region of the infarct, i. e., in the septum and in the left ventricle (Fig. 7). There were areas of marked fibrous replacement here. In the lateral wall of the left ventricle there also were areas of fibrous replacement, with less marked but very evident fatty degeneration and infiltration. The right ventricle appeared normal, except for a slight increase of connective tissue.

CASE 6.—A man, aged 46, who was admitted Sept. 5 and died Sept. 27, 1919, four weeks before admission had noticed swelling of both limbs, dyspnea on exertion, precordial pain and belching of gas. He had fluid in the right side of the chest ten days after admission. The apex beat was 12 cm. to the left

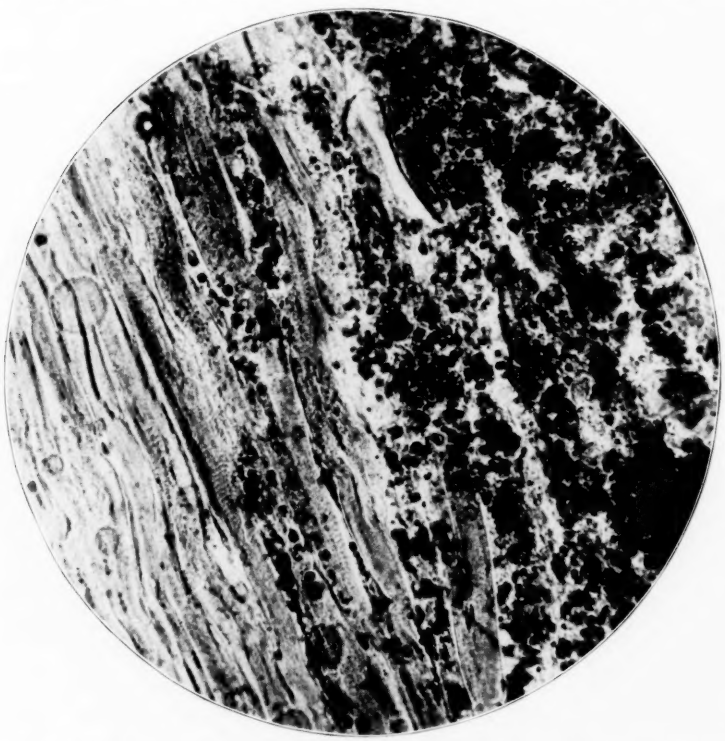


Fig. 7. (Case 5).—Fatty degeneration in infarcted area of heart muscle; the fatty granules appear black as scharlach r stain was used.

in the fifth space; there were no murmurs. The liver edge was palpable 5 cm. below the costal margin. The urine showed albumin; the specific gravity was 1.020, and there were hyaline casts. Phenolsulphonephthalein excretion was 46 per cent. in two hours, September 9; 15 per cent., September 19. The blood pressure was 125 systolic, and 85 diastolic. The nonprotein nitrogen was 65 mg.

The electrocardiogram nineteen days before death (Fig. 8) showed a Q-R-S group on the borderline of left ventricular predominance. The T wave was downward in Leads I and II (the patient had received scarcely any digitalis, only 90 minims of the tincture in the two days previous to the taking of the electrocardiogram). The excursions of the Q-R-S group were small, only 6 mm.

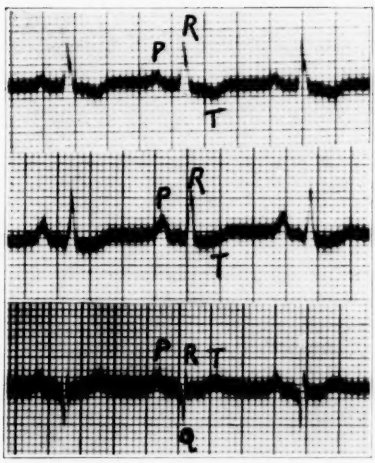


Fig. 8 (Case 6).—Downward T waves in Leads I and II; voltage of Q-R-S group rather low.

Fig. 9 (Case 6).—Section just beneath the pericardium, the subpericardial fat being visible at the top of the picture; marked increase of interstitial connective tissue; subpericardial tissue contains many round cells.

The necropsy diagnosis was acute dilatation of the heart; chronic myocarditis; atheroma of the aorta; lung infarct; serofibrinous pleurisy; chronic parenchymatous nephritis; chronic interstitial nephritis, and chronic passive congestion of liver.

The gross examination of the heart showed that it was much enlarged, weighing 875 gm. The wall of the right ventricle was thickened, but the left was thinned and small gray areas were scattered throughout it. All the valves were normal. The coronaries showed atheroma, which was marked in the left and for 3 cm. this artery was almost completely obliterated by firm calcareous deposits on its walls. The aorta showed many atheromatous patches, most numerous about the coronary orifices and for 4 cm. beyond the valve.

Microscopic examination revealed marked connective tissue increase between the muscle bundles of both ventricles, and in some areas the appearance of a fibrous replacement (Fig. 9). The subpericardial areolar tissue contained a good many round cells, budding capillaries and fibroblasts. There was no fatty degeneration.

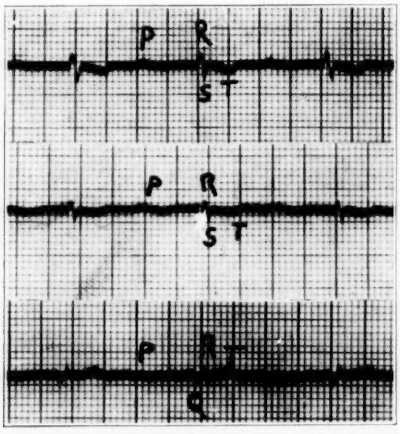


Fig. 10 (Case 7).—Record showing prolonged A-V conduction time, P-R measuring 0.32 second; low voltage of Q-R-S group; downward T waves in Leads I and II.

Case 7.—A man, aged 57, who was admitted March 3 and died April 25, 1921, entered the hospital with the complaint of dizziness, swelling and pain in the abdomen and legs. He gave a long history of alcoholism and for the last five years had had dyspnea and precordial pain on exertion, rarely accompanied by fainting attacks. The heart was enlarged, 13 cm. to the left of the midsternal line in the sixth space and 2 cm. to the right in the fourth space. The heart sounds were distant and very poor in quality. Extrasystoles were present with a slow rate of from 50 to 60. The blood pressure was 140 systolic, 90 diastolic. The urine showed a heavy trace of albumin, with hyaline and granular casts; the specific gravity was 1.020. The blood urea was 40 mg. per hundred cubic centimeters.

The electrocardiogram nineteen days before death (Fig. 10) showed a prolonged auriculoventricular conduction time, 0.4 second. All the waves were very small. The T wave was downward in Leads I and II. During the three days preceding the electrocardiogram, the patient had received 140 minims of tincture of digitalis and 2 ampules of a proprietary preparation of digitalis.

Necropsy findings were: chronic parenchymatous nephritis; kidney infarcts; general arteriosclerosis; chronic myocarditis (replacement fibrosis); hypertrophy of the heart; liver congestion, and chronic perisplenitis.

The gross examination of the heart showed a considerable increase of fatty tissue on the surface of the organ. The heart was much enlarged. The ventricular walls appeared normal but thinned, and there were no areas of fibrosis. The valves were negative, except very slight thickening of the edge of the mitral valve. The coronaries were markedly thickened and calcified and narrowed throughout.

The microscopic examination of the heart revealed considerable connective tissue replacement in the region of the left apex and also in the right ventricle. The septum showed a moderate degree of fibrous infiltration. There were a few

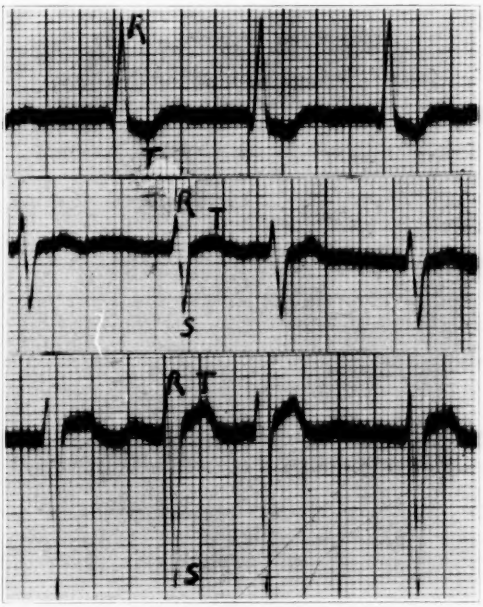


Fig. 11 (Case 8).—Auricular fibrillation; the Q-R-S group is abnormally wide and with notching or slurring in each lead; T is downward in Lead I.

small round cell foci in the pericardial surface of the left ventricle and, rarely, in the muscle itself. No fatty degeneration was present.

CASE 8.—A man, aged 61, who was admitted March 28 and discharged April 19, 1919, had had a doubtful history of tuberculosis at 21. He had had "heart trouble" for twenty-five years and swelling of limbs for nine months previous to admission, when he showed edema of the lower extremities, coughing spells and dyspnea. His heart was enlarged, 14 cm. to the left in the seventh space; the heart action was regular. The blood pressure was 130 systolic, and 70 diastolic. The nonprotein nitrogen was 43 mg. The urine showed a faint trace of albumin. The phenolsulphonephthalein output was 33 per cent. in two hours. The patient was treated with digitalis and discharged somewhat improved, but was readmitted with edema, cough and dyspnea, May 27, and died June 28.

The electrocardiogram six days before death (Fig. 11) showed auricular fibrillation and left ventricular predominance. The Q-R-S group had a duration of 0.12 second and notching in three leads. The T wave was downward in Lead I (possibly explained by the patient's digitalization, which was considerable, about 3½ ounces (104 c.c.) of the tincture having been given in the twenty-five days before the electrocardiogram was taken).

The necropsy diagnosis was: general arteriosclerosis; chronic myocarditis; coronary arteriosclerosis; hypertrophy and dilatation of the heart, and chronic passive congestion.

The gross examination of the heart showed that it was markedly enlarged, weighing 640 gm., with numerous small areas of fibrosis in the left ventricle. At the apex the wall was thinned and consisted almost wholly of fibrotic tissue with calcific deposits. The inner surface of this tissue had an attached thrombus.

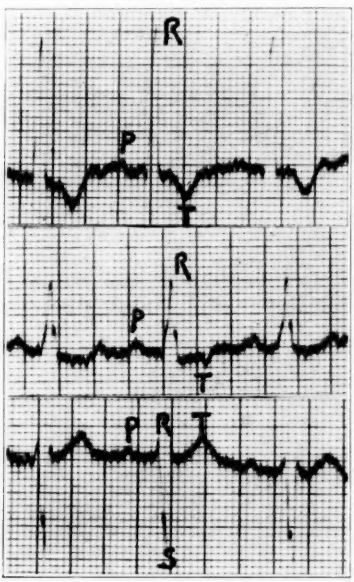


Fig. 12 (Case 9).—Record showing abnormally wide Q-R-S group (0.12 second) and notching or slurring in each lead; downward T wave in Leads I and II.

The endocardium showed a patchy sclerosis, especially marked in the apical and anterior part of the septum. The right ventricle, including the endocardium, appeared normal. There was marked atheroma of both coronaries, especially the left, the anterior descending branch being almost obliterated. The valves were practically negative.

Microscopic examination revealed a marked increase in the interstitial connective tissue in the left ventricle while in the right ventricle, where it was only slight, the walls of many of the blood vessels were thickened and occasionally obliterated. There was no fatty degeneration.

Case 9.—A man, aged 52, who was admitted Feb. 10 and discharged Feb. 22, 1920, was readmitted April 28 and died May 21. There had been a gradual onset of shortness of breath, anorexia, dyspnea and orthopnea after an attack of influenza in February, 1919. Edema developed during the second admission as did

palpitation and vomiting and a bronchopneumonia. The apex beat was 18 cm. to the left of the midline in the fifth space. The dulness extended 4 cm. to the right in the fourth space. The rate was rapid, and there was a long, blowing systolic murmur at the apex which was transmitted into the axilla. There was liver dulness 4 cm. below the costal margin. The blood pressure was 280 systolic, and 170 diastolic on the first admission, 170 systolic and 130 diastolic during the second. The specific gravity of the urine was from 1.010 to 1.020; albumin and granular casts were present. The blood urea was from 60 to 138 mg.

The electrocardiogram twenty-eight days before death (Fig. 12) showed a wide Q-R-S group with notching or slurring in all three leads. Left ventricular predominance was indicated. The T wave was downward in Lead I and zero in Lead II (the patient had received 480 minims of tincture of digitalis for one week and then 20 minims every day for the two weeks previous to the time the record was taken).

The necropsy findings were: chronic interstitial nephritis; hypertrophy of the heart; general arteriosclerosis; chronic passive congestion of the liver and kidneys; bronchopneumonia; gangrene of the lung, and chronic pleurisy.

The gross examination of the heart revealed a much enlarged organ, weighing 740 gm. Both ventricles were considerably hypertrophied. All the valves were normal. The coronaries showed extensive atheromatous placques but no narrowing of the lumen. The endocardium of the left ventricle was much thickened, particularly on the septum, and the endocardium of the right ventricle also was thickened.

The microscopic examination revealed a slight degree of fibrous tissue infiltration throughout the heart muscle, so slight that it could scarcely be considered abnormal. The endocardium was considerably thickened. A portion of the left bundle branch was seen in the section from the septum and seemed quite normal at that level. No fatty degeneration was present.

CASE 10.—A man, aged 70, between March 20, 1919, and his death, April 22, 1920, had five admissions to the New York Hospital, each time with the diagnosis of chronic interstitial nephritis and chronic myocarditis. Since 1913 the patient had had "heart and kidney trouble." He had swelling of the legs, precordial pain, dyspnea on exertion, cough, difficulty in urination and nocturia from three to four times a night. The heart rapidly enlarged from 9 cm. to the left of the midsternal line in the fourth space, in May, 1919, to 14 cm. in the sixth space on the last admission. There was a blowing systolic murmur at the apex, and a short systolic murmur at the aortic area. Edema of the penis, scrotum and legs was present. The heart action was totally irregular, and the liver was enlarged. The urine showed a faint trace of albumin on the first admission, and later a heavy trace, with hyaline casts; the specific gravity was 1.020. The blood pressure ranged from 140 systolic, 60 diastolic, to 160 systolic, 80 diastolic, and reached 200 systolic, 80 diastolic, on his last admission. The nonprotein nitrogen was 64 mg.

The electrocardiogram nine days before death (Fig. 13) showed abnormal ventricular complexes suggesting a partial bundle branch lesion.

At necropsy the diagnosis was: chronic interstitial nephritis; chronic cardiac valvular disease; chronic myocarditis (replacement fibrosis); cirrhosis of the liver; chronic passive congestion of the liver and spleen; general arteriosclerosis, and chronic prostatitis.

The gross examination of the heart showed a greatly hypertrophied and dilated organ, weighing 575 gm., with the mitral valves thickened along the edge and the aortic leaflets thickened and fused. The muscle of the left ventricle was thinned out toward the apex. The coronaries were tortuous and stiff, but not occluded, and there was endocardial thickening in the right ventricle between the anterior and the posterior papillary muscles, and in the left ventricle over the lower part of the septum.

The microscopic examination revealed a diffuse connective tissue growth between the cells, especially marked in the left ventricle, and also a fair number of dense fibrous patches in the left ventricle (Fig. 14). No fatty degeneration was present.

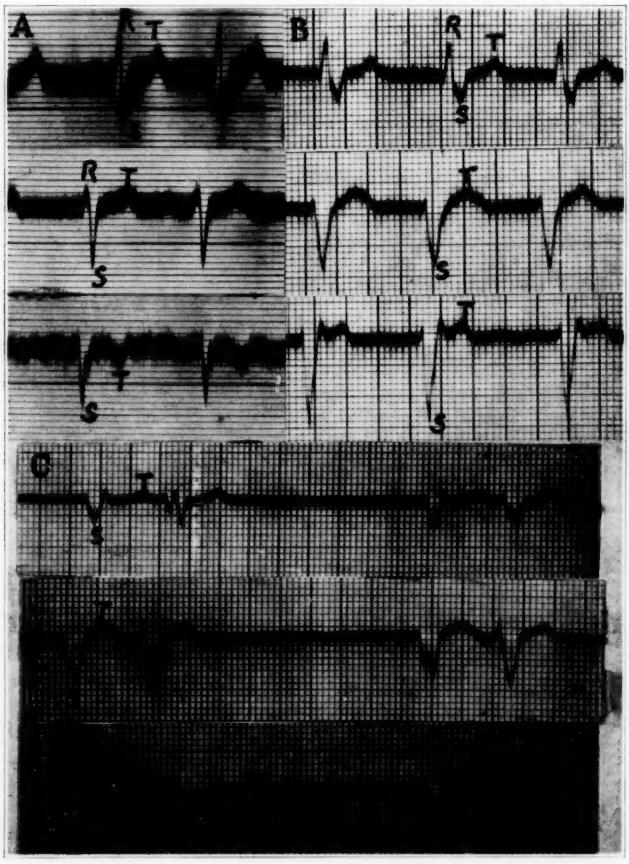


Fig. 13 (Case 10).—Auricular fibrillation in all records; *A*, record of December, 1915, showing an unusual Q-R-S group with deep S in all three leads; *B*, record of December, 1919, the ventricular complex now indicating bundle branch block, and *C*, record of April 13, 1920, showing complete heart block with ventricular premature beats. The ventricular complexes of the rhythmic beats indicate bundle branch block.

Case 11.—A man, aged 53, had complained of weakness for two years since an attack of pleurisy, with effusion, and shortness of breath commencing six weeks before admission to the hospital, June 2, 1920. There was a history of an old chancre, and the patient complained of a nonproductive cough, precordial pain, dyspnea, orthopnea, and edema of the legs. Physical examination showed

Fig. 14 (Case 10).—Dense patch of fibrous tissue in ventricular wall; replacement fibrosis.

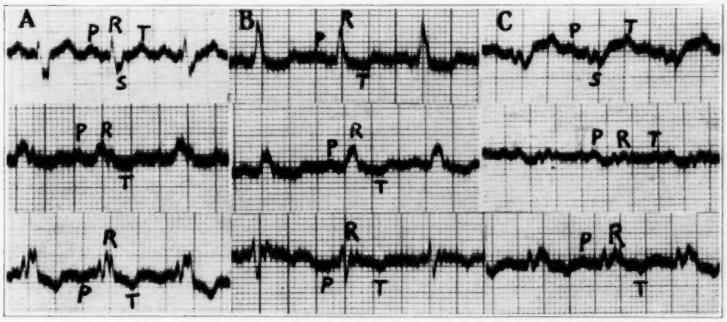


Fig. 15 (Case 11).—*A*, record of June 21, of the type associated with arborization block; *B*, record of August 11, less typical of arborization block, and *C*, record of September 30, the last record and quite typical of arborization block. All of these records show sinus rhythm.

the heart 14 cm. to the left in the sixth space. The sounds were irregular; extrasystoles and a low pitched systolic murmur were heard in the mitral area. The liver was palpable down to the umbilicus. The patient's chest was tapped repeatedly for fluid. The blood pressure was 130 systolic, 80 diastolic. The urine contained albumin, red blood corpuscles, and granular and epithelial casts; the specific gravity was 1.020.

The electrocardiogram taken one day before death (Fig. 15 *C*) showed a small Q-R-S group considerably notched and abnormally wide. The T wave was inverted in Leads II and III, but the patient had received no digitalis in two weeks. The electrocardiogram was of the type associated with arborization block.

The patient died, Oct. 1, 1920, four months after admission. At necropsy the diagnosis was: chronic interstitial nephritis; chronic valvular disease; hypertrophy of the heart; syphilis of the aorta; chronic passive congestion of the lungs, liver and spleen, and infarcts of the lungs.

The gross examination of the heart showed pericardial fluid and fibrin. The heart was large, weighing 475 gm., and the mitral valve was thickened and sclerosed. The muscle was soft and flabby. There was slight atheroma of the coronaries; the endocardium was normal.

Microscopic examination revealed a considerable degree of fibrous replacement through the heart, especially marked in the left ventricle. No fatty degeneration was present.

COMMENT

In the preliminary report [1] we considered that the first four of these patients had no significant abnormalities of the ventricular waves. The abnormal T waves in the first two cases were ascribed to the digitalis the patient had received.[7] This was probably the cause; still it is possible that the T wave may have been inverted in Leads I and II before the digitalis was given, so we cannot be certain that there was not a significant T wave abnormality in the records of these patients. The Q-R-S group, however, was normal in both these records.

Case 3 is an example of normal ventricular waves with little or no muscle abnormality. This practically normal ventricular muscle in the presence of evident valvular disease and a probably diseased auriculoventricular bundle also is of especial interest.

Patient 4 was considered to have normal Q-R-S waves in spite of the slightly prolonged duration, i. e., 0.12 second instead of 0.1. The heart was extremely large and the thickened wall of the left ventricle would require more time for the spread of the excitation process. For this reason a prolonged Q-R-S interval in this hypertrophied heart was considered normal. Further study of this case indicates that it is more likely that the prolongation of the Q-R-S group was not due to the size of the heart. Records taken, Dec. 27, 1920, Jan. 8, 1921, and January 25, had a Q-R-S group with a duration of 0.1 second, whereas that of Feb. 5, 1921, was the record discussed in the preliminary report. The heart was already greatly hypertrophied, January 25, and it could scarcely

7. Cohn, A. E.; Fraser, F. R., and Jamieson, R. A.: The Influence of Digitalis on the T Wave of the Human Electrocardiogram, J. Exper. Med. **21**:593, 1915.

have increased enough more in the eleven days before February 5 to have caused this change in the duration of the Q-R-S group. As a matter of fact the pericarditis noted at necropsy developed during this period and we now believe that the inflammatory invasion found in the outer ventricular layers was the cause of the delay in the spreading of the excitation and the prolongation of the Q-R-S group.[8]

Patient 5 had an infarct of the heart muscle on the posterior surface of the left ventricle, due to occlusion of the anterior descending branch of the left coronary artery. The electrocardiogram presented the peculiarity of the T wave which is often seen with coronary occlusion of rather recent date.[9]

The ventricular waves of Cases 6 and 7 have small excursions of the Q-R-S group and downward T waves in Leads I and II. Both hearts evidenced thinning of the wall of the left ventricle and, on microscopic examination, fibrous tissue infiltration between the muscle fibers; in areas a denser fibrous tissue had the appearance of replacement fibrosis. The coronary arteries of both these patients were markedly diseased and calcified in areas and the lumina were diffusely narrowed, in places almost closed. The myocardial changes were probably the result of the deficient blood supply. (The downward T waves of Case 7 might have been due to digitalis but the amount of the drug was scarcely sufficient to produce the change.)

Patient 8, whose record showed a large notched Q-R-S group and in Lead I a downward T wave, showed disease of the character and distribution that has been associated with "arborization block" curves.[4] The record of this patient does not show the typical "arborization block" features.

8. The records taken, February 5, before and after removal of 500 c.c. of pericardial fluid afford an interesting example of the effect of such fluid on the electrocardiogram and on the position of the heart.

	P-R Interval	Maximum Excursion Q-R-S	Angle Alpha for R_2	Maximum Excursion T Wave	Angle Alpha for T_2
Before tapping	0.20	8.5 mm.	70	2.0 mm.	60
After tapping	0.20	10.0 mm.	76	2.5 mm.	66

The lower voltage in the presence of the fluid may be due to short-circuiting of the electric current within the pericardial sac. The changes in the angle alpha (the angle between the horizontal and the axis of electric potential of the heart at any given moment) is probably due to the shifting of the position of the heart by the fluid. A similar decrease in the voltage has often been observed with pericardial effusion in the course of routine clinical records, but this is the only case that I have observed directly before and after tapping.—H. E. B. P.

9. Pardee, H. E. B.: An Electrocardiographic Sign of Coronary Artery Occlusion, Arch. Int. Med. **26**:244 (Aug.) 1920. Smith, F. M.: Electrocardiographic Changes Following Occlusion of the Left Coronary Artery, Arch. Int. Med. **32**:497 (Oct.) 1923.

In this connection a case reported by Drury [10] is important, for he, too, found a pathologic picture similar to ours and the electrocardiogram of his case failed to show any arborization block features. It is evident from these two hearts that the special pathology often associated with the arborization block features of the electrocardiogram may occur without causing the special electrocardiographic changes.[11]

The electrocardiographic curves of Case 11 had a small, widened and notched Q-R-S group and presented all the criteria of arborization block. The heart, however, did not have the typical pathologic findings which have been associated with that condition, e. g., no closure of the anterior descending branch of the left coronary artery; in fact, the atheroma here was slight. Nor were the fibrous changes accentuated in the endocardial or subendocardial layers; they were rather diffusely distributed but more marked in the left ventricle.

Case 11 shows that all the electrocardiographic criteria of arborization block may be present without the expected pathologic findings. Two of the cases reported by Oppenheimer and Rothschild [4] were also in this category. These authors emphasized the predominance of the pathologic changes in the endocardial and subendocardial layers as compared with the outer two thirds of the ventricular muscle. They considered that the former situation favored an involvement of the finer ramifications of the auriculoventricular conduction system. This endocardial and subendocardial distribution of the pathologic changes was evident in our Case 8 and in Drury's reported case, neither of which gave the typical curves.

Evidently the association of this special pathology and the special electrocardiographic features of "arborization block" is not a constant one, though the electrocardiographic changes have not occurred except in the presence of a considerable disease. It seems that a diffuse muscle disease, by causing an abnormal spreading of the contraction stimulus, may produce the notched and widened Q-R-S complex and prevent the development of the normal voltage of these waves, so that their amplitude is low. Such a diffuse disease will most commonly be secondary to coronary disease, though it may be primary, owing to rheumatic or syphilitic infection.

Though we believe that the low voltage of the waves in arborization block curves is usually the result of a diffuse disease, yet Case 8 is an exception to this association, having diffuse disease and large waves.

---

10. Drury, A. N.: Arborization Block, Heart **8**:23 (Feb.) 1921.

11. Drury's curve had only slightly abnormal ventricular waves. The Q-R-S was not notched and had a duration of 0.1 second. The waves had the following values: $R_1 = 6$ mm.; $S_1 = 0$; $R_2 = 6$ mm.; $S_2 = 3$ mm.; $R_3 = 5$ mm.; $S_3 = 5$ mm. The T wave was upward in Leads I and II. $T_1 = 0.7$ mm.; $T_2 = 0.7$ mm.; $T_3 = 0$.

A later record of his case was suggestive of right bundle branch block but without notching of Q-R-S.

The record of Case 9 presented a notching of the Q-R-S group with inversion of T_1 and T_2 while the ventricular muscle itself showed a diffuse but slight increase of connective tissue. The endocardium of both ventricles was thickened, especially on the septal surface of the left ventricle near the apex. Here then is a case in which the terminal ramifications of the bundle branch tissue may have been interfered with by the thickened endocardium, causing an abnormal spreading of the contraction stimulus. The abnormal T wave may be due to the same cause, for if the distribution of the contraction stimulus is sufficiently abnormal the T wave will be changed.[12] This case emphasizes another variety of electrocardiographic change which may result from an interference with the spreading of the contraction stimulus within the ventricles. It seems that we are unable to determine from the presence of a notched Q-R-S and an abnormal T wave whether there is a diffusely diseased ventricular muscle (Case 8) or endocardial fibrosis (Case 9), or whether both factors are present.

Case 10 illustrates another result of disease interfering with the spreading of the contraction. The earlier records, as in Drury's case, are not striking in their abnormality.[13] Records taken in September, 1919, in December, 1919, and April 13, 1920, shortly before death, showed the wide and notched Q-R-S of bundle branch block but did not have the typical direction of Q-R-S and T for either a right or a left bundle branch lesion.

This heart was the seat of extensive changes in the muscle, especially marked in the left ventricle where there were silvery patches of fibrosis throughout. Moreover, there was a fibrous thickening of the endocardium at the apical part of the septum in the left ventricle and in the region between the papillary muscles of the right ventricle. In either of these positions the branches of the auriculoventricular bundle may have been involved in the fibrosis. Here we have an extensively damaged muscle and possibly a damaged conduction system to account for the changes in the electrocardiogram.

Since all the patients of this series died of cardiac failure there is a certain clinical interest in the fact that two of the four hearts with valvular disease had quite a normal ventricular muscle, and only one of the four had much abnormality of the muscle. On the other hand,

12. Wilson, F. N., and Herrmann, G. R.: An Experimental Study of Incomplete Bundle Branch Block, Heart **8**:229 (May) 1921.

13. The record of December, 1915, was abnormal both in having a well developed S_3 with left ventricular predominance and in the notching of S_2. A record of May, 1916, showing left predominance but with a small S_3, would probably pass as normal. These records from a known case of disease suggest that if S_3 is present in records of left ventricular predominance it may have to be considered abnormal.

of the six arteriosclerotic hearts, all had a definitely abnormal muscle. The patients with valvular disease, it appears, died before the muscle was sufficiently affected to appear abnormal under the microscope so that the valvular damage must have been the chief factor in the heart failure. In the group with normal valves the muscle disease was extensive and was the evident cause of death in all but one case in which the patient, who had high blood pressure and uremia, died of bronchopneumonia (Case 9).

SUMMARY AND CONCLUSIONS

The outstanding feature of this study seems to us to be the variability of the electrocardiographic abnormality when extensive chronic lesions of the ventricular muscle are present. Cases 6, 7, 8, 10, 11 and that of Drury all showed extensive fibrosis of the ventricular muscle with most varied effects on the ventricular waves of the electrocardiogram. Drury's case and our Case 8 had the results of long standing occlusion of the descending branch of the left coronary artery, in effect an old scar, and in neither case was there a special electrocardiographic peculiarity. Case 6 showed a narrowing of this artery but not an occlusion and showed still different ventricular waves.

Even low voltage, which is usually associated with extensive lesions (Cases 6, 7, 10 and 11), was not found in Case 8, so that it is apparently not a constant result of widespread disease.

There has been apparently no specific relation between the type of electrocardiographic abnormality and the pathologic process found in the heart. There have been curves of arborization block which have not been associated with the special pathologic findings (Case 11) and, on the other hand, the special pathologic findings have appeared without these special curves (Case 8 and Drury's case).

The special T wave abnormality said to be associated with recent coronary artery closure has been again demonstrated in such a case (Case 5).

Pericarditis with effusion (Case 4) may possibly decrease the voltage of electrocardiographic waves and may prolong the Q-R-S duration if the inflammation extends into the ventricular muscle.

We have seen other necropsies since this series was first observed and we have not yet seen normal ventricular waves when more than a very slight abnormality of the ventricular muscle was demonstrable; nor have we seen extensive disease with normal waves.

In other words, an abnormal electrocardiogram of any of the types we have described is indicative of a diseased heart while a normal electrocardiogram is a sign of a fairly healthy muscle.

We believe that disease of the ventricular muscle plays the dominant rôle in producing abnormalities of the electrocardiographic curve by

causing an abnormal development of the electrical product of the contraction. If the conduction tissue becomes involved in disease of the endocardium this also may cause changes in the curve by causing an abnormal spreading of the contraction. Each of these factors will have a variable importance in any given case.

A COMPARISON OF ACUTE RHEUMATIC AND SUBACUTE BACTERIAL ENDOCARDITIS *

B. J. CLAWSON, M.D.
AND
E. T. BELL, M.D.
MINNEAPOLIS

A typical case of subacute bacterial endocarditis is characterized clinically by a septic temperature, physical signs of valvular heart disease, evidence of embolic processes (petechiae, embolic glomerulonephritis, etc.), and a positive blood culture (streptococcus). There is often a secondary anemia and moderate enlargement of the spleen, and death usually results within two years. On the other hand, the characteristic features of acute rheumatic endocarditis are acute arthritis, fever, evidence of valvular heart disease, absence of embolic processes, and a tendency to recover with or without a valve defect. Typical instances are therefore easily distinguished clinically, but there are many cases in which the diagnosis is uncertain.

The transition from the acute rheumatic to the subacute bacterial type may be so gradual that it is impossible to say where the one ends and the other begins. The following history illustrates such a case:

REPORT OF CASE

A white girl, aged 23, became ill, Jan. 15, 1924, with swelling, stiffness and tenderness of the joints (elbows, wrists, knees and ankles), fever and chills, dyspnea, palpitation and weakness. After two weeks in bed she returned to work, but was obliged to rest every few days. Sometimes she noticed edema in the ankles at the end of a day. She continued to have chills and fever, especially in the forenoon, and gradually grew weaker. She was admitted to the hospital, Feb. 18, 1924.

Seven years before admission she had an attack similar to this one except that it was more severe. At that time practically all the joints of the extremities were involved, and she was confined to bed for a month.

Physical examination, February 18, showed an enlarged heart with a systolic murmur at the apex. A friction rub could be heard at the right border of the sternum. The joints were swollen and tender. Two days after admission, petechiae were found on both extremities and the spleen was palpable for the first time. The hemoglobin on admission was 80 per cent. It gradually decreased until a few days before death, when it was 38 per cent. The number of red blood cells was reduced gradually from 4,700,000 to 2,000,000. The leukocytes ranged from 6,000 to 4,000. Two days after admission many red blood cells were found in the urine, and they continued to be present during the remainder of the course of the disease. The temperature ranged from 99 to 103. She gradually grew weaker and died, April 6, 1924. *Streptococcus viridans* was isolated in pure culture from the blood at different times before death and at necropsy. Necropsy revealed a typical anatomic case of subacute bacterial endocarditis with infarcts of the spleen and kidneys and embolic glomerulonephritis.

* From the Department of Pathology, University of Minnesota Medical School.

It is particularly difficult to distinguish a so-called mild case of subacute bacterial endocarditis from the rheumatic form. With improved methods of isolating bacteria from the blood a high percentage of positive cultures may be obtained from cases of typical rheumatic endocarditis. Apparently, this may be the explanation of the increasing number of reports of recovery from subacute bacterial endocarditis. Not infrequently the original clinical diagnosis is changed from rheumatic to subacute bacterial endocarditis or vice versa to fit the subsequent progress of the case. From a study of a large number of cases one gets the impression that these two forms of endocarditis represent mild and severe degrees of the same infection. Miller [1] expressed this idea in speaking of mild cases of subacute bacterial endocarditis when he said that formerly he would have diagnosed such cases rheumatic endocarditis. Biggs [2] states that, clinically, many cases of subacute bacterial endocarditis cannot be distinguished from rheumatic endocarditis.

In this paper the division of fatal cases of endocarditis into the acute rheumatic and the subacute bacterial types is based on the clinical course and the gross anatomic character of the vegetations—whether small, smooth and hard (rheumatic) or large, soft and villous (subacute bacterial). A comparison of the two types is made in respect to: (1) the blood picture, (2) the gross and microscopic anatomic characteristics, and (3) the bacteriology.

Eighty cases of subacute bacterial endocarditis that came to necropsy are compared with thirty-five cases of rheumatic endocarditis, eighteen of which came to necropsy. The remaining seventeen are typical cases of rheumatic endocarditis clinically, and *Streptococcus viridans* was isolated from all of them.

BLOOD PICTURE

Leukopenia and Leukocytosis.—A leukopenia may occur in subacute bacterial endocarditis, and this fact probably explains the occasional confusion with influenza, typhoid fever, malaria and incipient tuberculosis. The total leukocyte count has been suggested as a means of differentiating subacute bacterial from rheumatic endocarditis. The data available in our cases are analyzed in Table 1. It will be noted that a leukopenia (below 6,000) is present in four of the subacute bacterial group but not in any of the rheumatic cases. A definite leukocytosis (above 15,000) is found in 50 per cent. of the rheumatic and in 39 per cent. of the subacute bacterial cases. On the whole, the

1. Miller, Joseph, in discussion of Kilgore, E. S.: Arrhythmia of Auricular Fibrillation, abstr., J. A. M. A. **82**:1722 (May 24) 1924.

2. Biggs, A. D.: Prognosis of Chronic Infectious Endocarditis, Arch. Int. Med. **35**:402 (March) 1925.

leukocyte count is slightly lower in the subacute bacterial than in the rheumatic endocarditis, but it is of little value in differentiating the two types.

Anemia.—Anemia of the secondary type has been mentioned by various workers as characteristic of subacute bacterial endocarditis and has been considered of value in differentiating it from acute rheumatic endocarditis. A hemoglobin determination of nineteen of the thirty-five cases of acute rheumatic endocarditis is recorded. In only six cases does the hemoglobin drop below 80 per cent., and in only one is it below 60 per cent. (Table 1). On the other hand only 20 per cent. of the cases of subacute bacterial endocarditis have a hemoglobin percentage of more than 80 per cent., and in 33 per cent. the hemoglobin is below 60. The reduction in number of red blood cells corresponds

TABLE 1.—*Comparison of Rheumatic and Subacute Bacterial Endocarditis as Regards the Leukocyte Count, Hemoglobin and Erythrocyte Count*

	Acute Rheumatic Type		Subacute Bacterial Type	
	Number	Per Cent.	Number	Per Cent.
Leukocytes:				
15 to 25 thousand per c.mm.	10	50	19	39
10 to 15 thousand per c.mm.	5	25	15	31
8 to 10 thousand per c.mm.	3	15	5	10
6 to 8 thousand per c.mm.	2	10	6	12
Below 6 thousand per c.mm.	0	0	4	8
Total	20	..	49	..
Hemoglobin:				
80 to 100 per cent.	13	68	9	20
60 to 79 per cent.	5	26	21	47
Below 60 per cent.	1	5	15	33
Total	19	..	45	..
Erythrocytes:				
4.5 to 5 million per c.mm.	11	65	13	30
3.5 to 4.5 million per c.mm.	5	29	15	35
Below 3.5 million per c.mm.	1	6	15	35
Total	17	..	43	..

with the reduction in the hemoglobin (Table 1). In the subacute bacterial type, the degree of anemia increases with the progress of the disease. A severe anemia points strongly to the subacute form, but there may be only a moderate anemia in early stages.

ANATOMIC CHARACTERISTICS

Valves Involved.—The involvement of valves in order of frequency in the eighteen rheumatic cases is: The mitral alone, eight (44.5 per cent.); the aortic alone, none; the mitral and aortic, two (11 per cent.); the mitral and tricuspid, three (16.5 per cent.); the aortic and tricuspid, three (16.5 per cent.); the mitral, aortic and tricuspid, one (5.5 per cent.), and the mitral, aortic, tricuspid and pulmonary, one (5.5 per cent.) (Table 2). In the eighty cases of subacute bacterial endocarditis,

the valves involved are: the mitral alone, thirty (37.5 per cent.); the aortic alone, twenty-three (29 per cent.), and the mitral and aortic, nineteen (24 per cent.). Other combinations are rare. The number of acute rheumatic cases is too small for a satisfactory statistical comparison, but assuming that practically all old healed valves are produced by previous rheumatic infections, it is of interest to note that the three chief combinations of valvular involvement are about the same in rheumatic and in subacute bacterial cases. The order of frequency, which varies slightly from that in the subacute bacterial, is: the aortic and mitral, forty-seven (41 per cent.); the mitral, thirty-four (29.5 per cent.), and the aortic, twenty-one (18 per cent.). In either group the aortic and mitral are the only valves involved to any extent, although the involvement of the tricuspid in the acute rheumatic cases is relatively frequent. It is important to observe that the involvement of the aortic

TABLE 2.—*Frequency of Involvement of the Various Valves in Acute Rheumatic and Subacute Bacterial Endocarditis and in Old Valve Defects*

	Acute Rheumatic Endocarditis, 18 Cases		Subacute Bacterial Endocarditis, 80 Cases		Old Valve Defects, 115 Cases	
	Number	Per Cent.	Number	Per Cent.	Number	Per Cent.
Mitral	8	44.5	30	37.5	34	29.5
Aortic	0	0	23	29	21	18
Tricuspid	0	0	3	4	0	0
Mitral and aortic	2	11	19	24	47	41
Mitral and tricuspid	3	16.5	2	2.5	4	3.5
Aortic and tricuspid	3	16.5	1	1	0	0
Mitral, aortic and tricuspid	1	5.5	2	2.5	7	6
Mitral, aortic, tricuspid, pulmonary	1	5.5	0	0	1	0.9
Total mitral	15	83	53	66	93	81
Total aortic	7	39	45	56	76	66
Total tricuspid	8	44	8	10	12	10
Total pulmonary	1	5.5	0	0	1	0.9

alone is of not infrequent occurrence. The order of involvement of valves offers nothing of differential significance between subacute bacterial and acute rheumatic endocarditis.

Gross Vegetations.—In endocarditis immediately associated with acute rheumatic fever (rheumatic endocarditis, simple verrucous endocarditis), the heart valves on gross examination show small, smooth, globular nodules at the points of contact of the leaflets and on their free margins. Usually, these vegetations are not extensive enough to interfere seriously with the function of the valve.

The chief lesions found on the valves in subacute bacterial endocarditis are soft villous vegetations. These vegetations do not have the smooth surfaces found on the vegetations in acute rheumatic endocarditis. The consistency and size of the subacute bacterial vegetations make it easily possible for particles to break loose into the blood stream and produce the embolic processes so commonly found in subacute bacterial endocarditis.

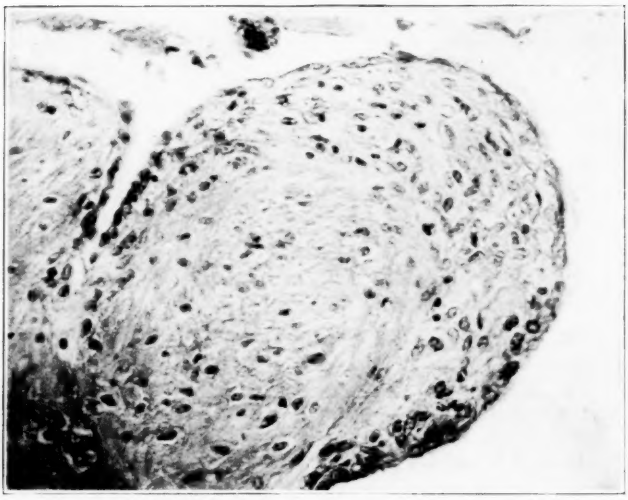


Fig. 1.—Early rheumatic vegetation.

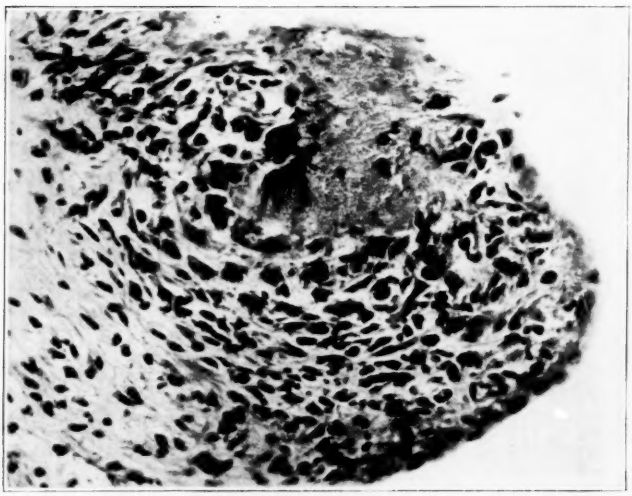


Fig. 2.—Early rheumatic vegetation showing a small thrombotic mass and rupture of endothelium.

Vegetations characteristic of the rheumatic type may generally be found on the same cusps with the vegetations of the subacute bacterial type. Acute rheumatic vegetations may be present on the cusps on one valve while on another there may be subacute bacterial lesions.

Microscopic Appearance of Vegetations.—Microscopically, the rheumatic vegetations show inflammation, chiefly proliferative in character, but containing a few polymorphonuclear leukocytes and many large cells having one or more vesicular nuclei similar to those found in the Aschoff nodules in the myocardium. Small masses of fibrin, a little serous exudate, and sometimes areas of necrosis are present (Figs. 1 and 2). The inflammatory process begins within the substance of the leaflet and extends to the surface, frequently causing desquamation of the endothelium. A small amount of thrombotic material is generally found, but it is not sufficient to cause a gross roughening or the detachment of particles with the production of embolic processes (Fig. 3).

TABLE 3.—*Mural Endocarditis, Pericarditis and Enlargement of the Spleen in Acute Rheumatic and Subacute Bacterial Endocarditis and in Old Valve Defects*

	Acute Rheumatic Endocarditis, 18 Cases		Subacute Bacterial Endocarditis, 80 Cases		Old Valve Defects, 115 Cases	
	Number	Per Cent.	Number	Per Cent.	Number	Per Cent.
Auricle	4	40	9	11	0	0
Ventricle	0	0	17	21	0	0
Auricle and ventricle	0	0	6	7.5	0	0
Total mural endocardial involvement	4*	40	32	40	0	0
Pericarditis	13	72	18	22.5	21	18
Spleen 450 gm. or more	1	5.5	19	24	..	..

* Ten were examined.

The condition of the valve is in reality a valvulitis as well as an endocarditis. This inflammatory condition of the cusps is typical in the eighteen cases of acute rheumatic endocarditis coming to necropsy.

Microscopically, the leaflets in the thirty cases of subacute bacterial endocarditis studied showed a valvulitis similar to that found in the leaflets in acute rheumatic endocarditis (Figs. 4 and 5). On the endocardial edge of the inflammatory area of the subacute bacterial valve, there is a platelet thrombus which is more extensive than that found in the acute rheumatic valve. As a rule, masses of streptococci are found in the thrombotic mass in the subacute bacterial type, but few or none are found in the active proliferative area. The condition of the valve in subacute bacterial endocarditis is essentially a valvulitis mostly proliferative in character, as in acute rheumatic endocarditis, but in addition having an adherent infected thrombotic mass. This addition of the larger infected thrombotic mass distinguishes the subacute bacterial vegetation from the acute rheumatic vegetation and seems to be a difference in degree of involvement.

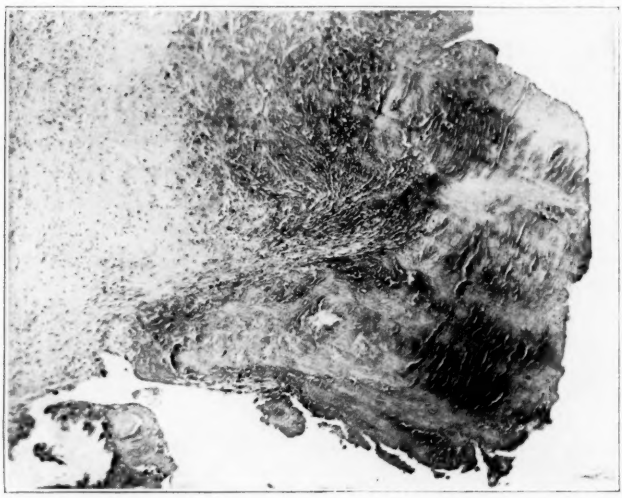


Fig. 3.—Rheumatic vegetation with more extensive thrombotic mass.

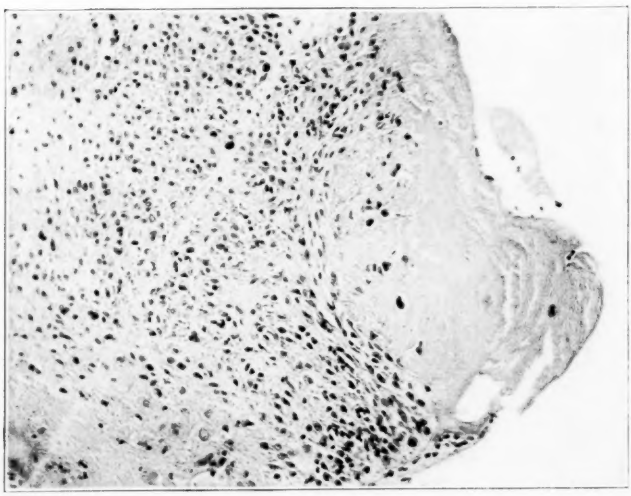


Fig. 4.—Vegetation in subacute bacterial case showing an inflammatory reaction similar to that in rheumatic vegetations.

Mural Endocardium.—The involvement of the mural endocardium has been described as a characteristic of subacute bacterial endocarditis. MacCallum [3] states that he not infrequently finds a thickening of the auricles with a fibrinous exudate over the thickened area in acute rheumatic hearts. We have found auricular involvement corresponding to the lesions described by MacCallum in 40 per cent. of the rheumatic cases examined (Table 3). The structure of these mural endocardial lesions was similar to the rheumatic vegetations. In the eighty cases of subacute bacterial endocarditis, the auricular endocardium alone was involved in nine (11 per cent.); the ventricular endocardium alone in seventeen (21 per cent.), and both the auricle and the ventricle in six (7.5 per cent.). In all, there was involvement of the mural endocardium in thirty-two (40 per cent.). The mural endocardial involvement in subacute bacterial endocarditis shows lesions corresponding to subacute bacterial vegetations. This involvement is believed by Murray [4] to result, in most cases, from direct extension from the valve and from the repeated contact of the infected vegetation with the mural endo-

TABLE 4.—*Myocardial Lesions Associated with the Different Forms of Endocarditis*

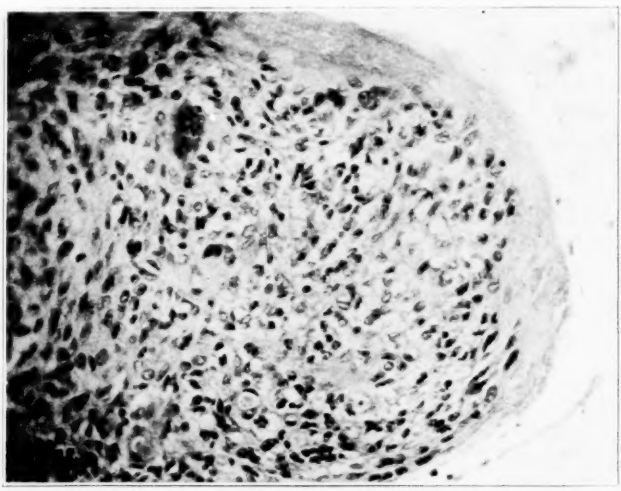
Type	Number Examined	Myocarditis of All Types		Aschoff Nodules		Proliferative Lesions		Exudative Lesions	
		Number	Per Cent.	Number	Per Cent.	Number	Per Cent.	Number	Per Cent.
Acute rheumatic	18	18	100	14	78	18	100	0	0
Subacute bacterial	61	14	23	7	11.5	53	86	9	14
Experimental streptococcic	13	10	77	2	15	13	100	0	0

cardium. The character of the lesions in the auricular endocardium in rheumatic cases suggests, however, that at least some of the mural endocardial lesions may be extensions from subendocardial infections. Involvement of the mural endocardium is found in both types of endocarditis and is therefore not a differential feature.

Myocardium.—Acute myocarditis other than that found with acute rheumatic endocarditis is rare. The type of inflammation illustrated by the Aschoff nodule or the rheumatic subcutaneous nodule has in general come to be considered a specific type of inflammation characteristic of the rheumatic virus. Libman [5] found these bodies in eighteen (32.1 per cent.) of fifty-six cases of rheumatic endocarditis. Thayer [6] found acute myocarditis in twenty-two (88 per cent.) of twenty-five cases of acute rheumatic endocarditis. Aschoff nodules were present in twenty-one (87.5 per cent.) of twenty-four cases examined.

3. MacCallum, W. G.: Bull. Johns Hopkins Hosp. **35**:329 (Oct.) 1924.
4. Murray, L. M.: Ann. Clin. Med. **1**:18 (July) 1922.
5. Libman, E.: Characterization of Various Forms of Endocarditis, J. A. M. A. **80**:813 (March 24) 1923.
6. Thayer, W. S.: Bull. Johns Hopkins Hosp. **36**:99 (Feb.) 1925.

In the eighteen cases of acute rheumatic endocarditis in our series coming to necropsy, myocarditis was present in all (100 per cent.) (Table 4). The Aschoff nodule was found in fourteen (78 per cent.). In seven of the sixty-one cases of subacute bacterial endocarditis examined (11.5 per cent.), the Aschoff nodule was present. In two of these, the tricuspid valve showed typical rheumatic vegetations, while subacute bacterial vegetations were present on other valves. Two cases were typical examples showing a continuous transition from acute rheumatic fever to subacute bacterial endocarditis. The other three cases were in persons in the first and second decades of life. The course of the disease was short and in two there was a history of rheumatism.



Fg. 5.—Vegetation in subacute bacterial case showing an inflammatory reaction similar to that in rheumatic vegetations.

Definite active inflammation was found in fourteen (23 per cent.) of the sixty-one cases of subacute bacterial endocarditis (Table 4). In all but two of the fourteen the inflammation was proliferative in character, with some large mononuclear and multinucleated cells. In these two cases, polymorphonuclear leukocytes were found which suggested that the lesions were embolic in character.

It is obvious that the type of inflammation represented by the Aschoff nodule is of more frequent occurrence in acute rheumatic endocarditis. The necropsy reports of such hearts are relatively small as it is unusual for death to occur at this stage. If the Aschoff nodule represents a specific type of reaction to the rheumatic virus, then the nodules evidently disappear rapidly since they are so infrequently found

in cases of subacute bacterial endocarditis (11.5 per cent.) and in cases of healed defective valves (8.5 per cent.) which are known to have had rheumatic infections.

Pericarditis.—The greater frequency of pericarditis with acute rheumatic endocarditis than with subacute bacterial endocarditis has been emphasized by various workers. This is true if we base our statistics on the necropsy findings in the subacute bacterial and rheumatic types. Acute rheumatic endocarditis, however, usually does not result in death and when it does pericarditis is one of the usual causes of death. Statistics concerning the relative frequency of pericarditis can be obtained more accurately if we compare subacute bacterial endocarditis with the cases in which death is due to old valve defects, since there is a general agreement that defective valves for the most part result from previous rheumatic infections. In the eighty cases of subacute bacterial endocarditis, pericarditis was found in eighteen (22.5 per cent.) (Table 3). It was present in thirteen (72 per cent.) of the eighteen cases of acute rheumatic endocarditis. In the 115 cases of healed defective valves pericarditis was present in twenty-one (18 per cent.). It is seen that the frequency of pericarditis in cases of acute rheumatic endocarditis coming to necropsy is high. It is also noted that the frequency of pericarditis in subacute bacterial endocarditis and in cases with healed defective valves coincides closely. The comparison is not exact since 59 per cent. of the subacute bacterial group apparently developed on old healed defective valves (probably of rheumatic origin), but the comparison does show that the frequency of pericarditis with rheumatic endocarditis is not high. It appears from these considerations that an associated pericarditis should not be considered a differential feature between the subacute bacterial and the rheumatic types.

Embolic Processes.—It may be safely said that embolic phenomena never occur in acute rheumatic endocarditis. In rare cases in heavy infections, petechiae may be noted but, as Gibson[7] pointed out, too much diagnostic importance must not be placed on petechiae even when they are found in recurrent crops for they may be present in nonembolic pathologic conditions such as septicemia.

In the eighty cases of subacute bacterial endocarditis, sixty-five (80 per cent.) showed the presence of embolic processes (Table 5). These were distributed as follows: petechiae, thirty (37.5 per cent.); infarcts of spleen, thirty-nine (49 per cent.); infarcts of kidney, thirty-two (40 per cent.), and infarcts of the brain, thirteen (16 per cent.). If the embolic processes are considered on the basis of infarcts of spleen, kidneys and brain, there were fifty-one (64 per cent.) which showed embolic phenomena. In the eighteen cases of rheumatic

7. Gibson, A. G.: Brit. M. J. **2**:308 (Aug. 28) 1920.

endocarditis, petechiae were reported in two (11 per cent.). There were no other embolic phenomena. Embolic glomerulonephritis was found in forty-two (58 per cent.) of seventy-two cases of subacute bacterial endocarditis, but in none of the eighteen acute rheumatic cases. The demonstration of embolic processes either clinically or anatomically affords a definite differentiation from rheumatic endocarditis; but it is to be remembered that this feature depends on the structure of the valvular vegetations, i. e., whether they are soft and villous or firm and smooth. It is probably a difference in degree rather than in the type of lesion.

Enlarged Spleen.—The spleen was found to weigh 450 gm. or more in nineteen (24 per cent.) of the subacute bacterial group and in one (5.5 per cent.) of the acute rheumatic group (Table 3). Therefore, a definitely enlarged spleen suggests the subacute form of endocarditis; but the absence of this finding is of little value in the differential diagnosis. The increased size of the spleen may be due in part to passive

TABLE 5.—*Embolic Phenomena Associated with Endocarditis*

	Acute Rheumatic Endocarditis, 18 Cases		Subacute Bacterial Endocarditis, 80 Cases	
	Number	Per Cent.	Number	Per Cent.
Petechiae	2	11	30	37.5
Infarct of spleen	0	0	39	49
Infarct of kidney	0	0	32	40
Infarct of brain	0	0	13	16
Embolic glomerulonephritis	0	0	42*	58
Total embolic processes	2	11	65	80
Infarction of spleen, kidney or brain	0	0	51	64

* Seventy-two were examined.

congestion, but seems to be caused largely by hyperplasia resulting from infection.[8]

BACTERIOLOGY

The work of many investigators, Swift and Kinsella,[9] Horder,[10] Libman,[11] Gow,[12] Curschmann,[13] Boyd,[14] Murray and Lougheed[15] and others, has demonstrated that subacute bacterial endocarditis is caused by streptococci, usually the viridans strains; but there is still no general agreement concerning the etiology of acute rheumatic endocarditis.

8. Arnett, J. H.: Am. J. M. Sc. **163**:590 (April) 1922.
9. Swift, H. F., and Kinsella, R. A.: Bacteriologic Studies in Rheumatic Fever, Arch. Int. Med. **19**:381 (March) 1917.
10. Horder, T. J.: Brit. M. J. **2**:301 (Aug. 28) 1920.
11. Libman, E.: Brit. M. J. **2**:304 (Aug. 28) 1920.
12. Gow, A. E.: Brit. M. J. **2**:307 (Aug. 28) 1920.
13. Curschmann, H.: München. med. Wchnschr. **69**:419 (March 24) 1922.
14. Boyd, F. D.: Edinburgh M. J. **27**:129 (Sept.) 1921.
15. Murray, L. M., and Lougheed, G. W.: Canad. M. A. J. **11**:666 (Sept.) 1921.

Streptococci have been isolated from the blood, the joints or the pericardial exudate in cases of acute rheumatic fever by Westphal, Wassermann and Malkoff,[16] Poynton and Paine,[17] Beaton and Walker,[18] Walker and Ryffel,[19] Loeb,[20] Camisa,[21] Beattie and Yates,[22] Collins,[23] Rosenow,[24] LaFetra,[25] Swift and Kinsella,[9] Quigley [26] and others.

Positive bacteriologic findings are recorded in thirty-two of the eighty cases of subacute bacterial endocarditis (Table 6). Of these strains five were hemolytic, twenty-two belonged to the viridans group, and five were not tested on blood agar. In eleven of the eighteen cases of acute rheumatic endocarditis coming to necropsy, an effort was made to isolate organisms. In nine a streptococcus was found. In five of these cases, it was found in the blood; in two, in the pericardial fluid; in one, in the pericardial fluid and spleen, and in one, in the blood before death and in the pericardial fluid at necropsy. In seventeen other cases the organism was isolated from living patients, once from the pericardial fluid, twice from the joints, and fourteen times from the blood. In all, streptococci were isolated in twenty-six cases of acute rheumatic fever and endocarditis. Twenty-four of these

TABLE 6.—*Bacteriology*

Type of Endocarditis	Number of Positive Cases	Streptococcus Viridans	Streptococcus Hemolyticus	Action on Blood Not Determined	Blood Before Death	Blood at Necropsy	Pericardial Fluid	Joints
Acute rheumatic.....	26	24	2	′	15	6	5	2
Subacute bacterial.....	32	22	5	5	18	14	..	..

strains belonged to the viridans group and two to the hemolytic group. It is seldom possible to recover these organisms in less than ten days of incubation at 37 C.[27] It has been our experience that if the blood for culture is taken when the temperature is high the organism can be isolated in more than 50 per cent. of the cases.

When compared with eleven of the twenty-five rheumatic strains, three subacute bacterial strains were found to agree in general in morphology, cultural characteristics, immune reactions, and in ability to produce experimental endocarditis in rabbits.[27]

16. Westphal, Wassermann and Malkoff: Berl. klin. Wchnschr. **36**:638, 1899.
17. Poynton, F. J., and Paine, A.: Lancet **2**:861, 1900.
18. Beaton, R. M., and Walker, E. W. A.: Brit. M. J. **1**:237, 1903.
19. Walker, E. W. A., and Ryffel, J. H.: Brit. M. J. **2**:659, 1903.
20. Loeb, L. M.: Arch. Int. Med. **2**:266 (Oct.) 1908.
21. Camisa, G.: Centralbl. f. Bakteriol. **57**:99, 1910.
22. Beattie, J. M., and Yates, A. G.: J. Path. & Bacteriol. **17**:538, 1912.
23. Collins, J. R.: Brit. M. J. **1**:220, 1913.
24. Rosenow, E. C.: J. Infect. Dis. **14**:61, 1914.
25. LaFetra, L. E.: Arch. Pediat. **32**:135, 1915.
26. Quigley, W. J.: J. Infect. Dis. **22**:198 (March) 1918.
27. Clawson, B. J.: J. Infect. Dis. **36**:444 (May) 1925.

Two groups of organisms were found by agglutination, dilution 1:10,000 (Table 7). Seven rheumatic serums showed fairly uniform agglutination results with the fourteen organisms tested and represented a homogeneous group. No agglutination occurred with the remaining rheumatic serums except with their homologous strains. These were representatives of a heterogeneous group. Three subacute bacterial serums were tested with the same fourteen organisms. Two of these serums fell into Group 1 and one into Group 2. Agglutination in high dilutions apparently does not differentiate strains of rheumatic origin from strains of subacute bacterial origin.

Tunnicliff [28] found an increased opsonic content for streptococci in the blood of rheumatic patients. In the serums of seven cases out of

TABLE 7.—*Agglutinations, 1: 10,000*

	Organisms													
	Rheumatic Origin											Subacute Bacterial Origin		
Serums of Rheumatic Origin	1	2	4	5	6	8	9	11	13	16	17	7	15	19
2	+	+	+	+	+	—	+	+	+	+	+	+	+	—
6	+	+	+	+	+	—	+	—	+	+	+	+	+	—
13	+	+	+	+	+	+	+	—	+	+	+	+	+	+
9	+	+	—	+	+	+	+	—	+	—	+	+	+	+
5	+	+	+	+	+	—	+	—	+	—	+	+	+	—
17	+	+	+	+	+	—	+	—	+	—	+	+	+	—
1	+	+	—	+	—	—	+	—	+	+	+	+	+	—
4	—	—	+	—	—	—	—	—	—	—	—	—	—	—
8	—	—	—	—	—	—	—	—	—	—	—	—	—	—
11	—	—	—	—	—	—	—	+	—	—	—	—	—	—
Serums of Subacute Bacterial Origin														
19	—	—	—	—	—	+	—	—	—	—	—	—	—	+
7	+	+	+	+	+	—	+	—	+	+	+	+	+	—
15	+	+	+	+	+	—	+	+	+	—	+	+	+	—

twelve, she found agglutinins for the same organisms. In all of twelve cases of subacute bacterial endocarditis, Kinsella [29] found agglutinins. Swift and Kinsella [9] were not able to find agglutinins (dilutions, 1:40) in the blood in five cases of rheumatic fever. We have tested seven serums from rheumatic fever patients. Five showed agglutinins in dilutions of 1:50. These positive serums agglutinated organisms isolated from acute rheumatic fever, chorea and subacute bacterial endocarditis. The presence of these agglutinins in the patients' serums suggests the streptococcus as the exciting agent in the etiology of rheumatic fever and also shows a relation between these strains and subacute bacterial strains.

28. Tunnicliff, R.: J. Infect. Dis. **6**:346, 1909.

29. Kinsella, R. A.: Streptococcus Endocarditis, Arch. Int. Med. **19**:367 (March) 1917.

When injected into rabbits, nine strains of rheumatic origin and one of subacute bacterial origin produced endocarditis grossly and microscopically similar to human rheumatic endocarditis (Fig. 6). One rheumatic strain produced in addition a typical subacute bacterial lesion with embolic processes in the kidney. From what was found in experimental endocarditis and myocarditis there is reason to believe that the myocarditis associated with acute rheumatic endocarditis is caused by streptococci. In ten of the thirteen cases of experimental endocarditis produced in rabbits by injecting streptococci, myocarditis was present (Table 4). The inflammation consisted of diffuse and nodular proliferative lesions with a slight degree of exudation (Fig. 7). In some areas a small amount of necrosis was present. The lesions contained

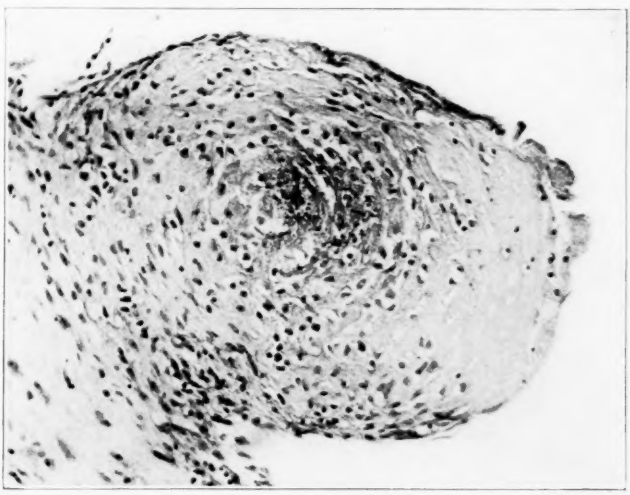


Fig. 6.—Vegetation in experimental streptococcic endocarditis (rabbit).

large mononuclear and multinucleated cells with vesicular nuclei. Some of the nodular lesions were similar morphologically to Aschoff nodules in cases of human rheumatic carditis (Fig. 8).

On the basis of morphology, cultural characteristics, agglutination tests and ability to produce experimental endocarditis, there is a suggestion that streptococci are responsible not only for subacute bacterial endocarditis but for acute rheumatic endocarditis.

Clinically, the two types of endocarditis under discussion were usually distinct but transition forms were occasionally seen. The clinical differences corresponded to the severity of the infection and the structural changes in the valves. Histologic studies of the valve leaflets indicated also that the two forms of endocarditis differ only in the intensity of the inflammatory reaction.

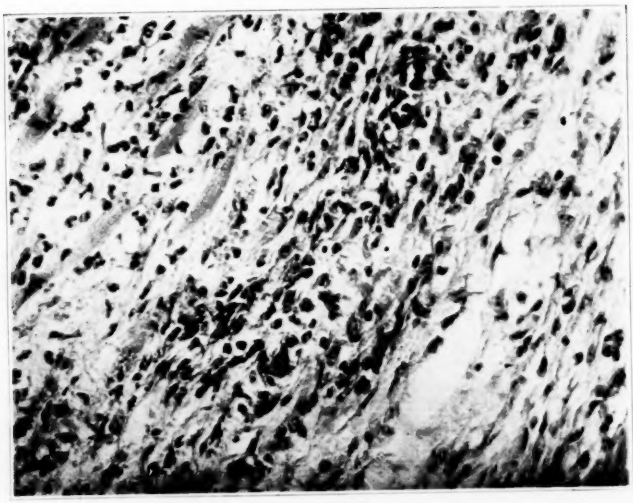


Fig. 7.—Experimental streptococcic myocarditis (rabbit).

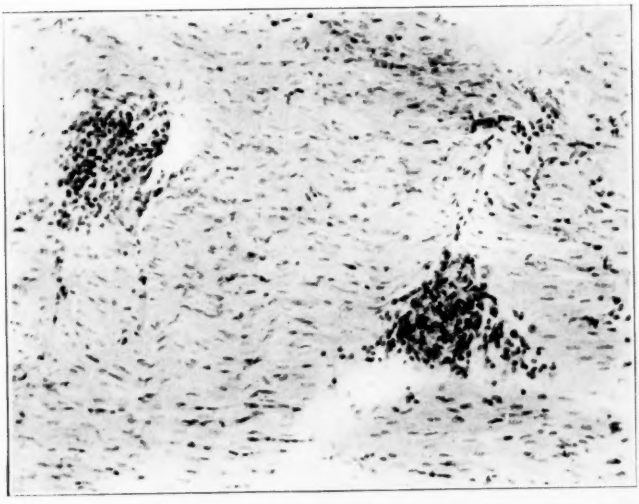


Fig. 8.—Nodular lesions in the myocardium (rabbit) resembling Aschoff nodules.

SUMMARY

The leukocyte count is of little value in differentiating rheumatic from subacute bacterial endocarditis.

A severe secondary anemia strongly suggests the subacute bacterial type.

The order of frequency of valvular involvement is essentially the same in both forms.

In both types there is a proliferative inflammation in the valve, but the thrombus over the infected area is larger and softer in the subacute lesion. The differences are in degree rather than in kind. Typical rheumatic vegetations may be found with subacute vegetations on the same leaflet.

Myocarditis is more frequent in the acute rheumatic cases that come to necropsy.

Pericarditis seems to occur with practically the same frequency in rheumatic and in subacute bacterial endocarditis.

The frequent presence of embolic phenomena in the subacute bacterial type depends on the degree of involvement of the infected valves.

Mural endocardial involvement occurs with about the same frequency in both types but is more extensive in the subacute bacterial.

The finding of bacteria in the blood stream in endocarditis does not necessarily indicate the presence of the condition clinically recognized as subacute bacterial endocarditis.

Experimental endocarditis and myocarditis similar to human rheumatic lesions can be produced in rabbits by injecting streptococci.

The streptococci, generally the viridans strains, seem to be responsible for both rheumatic and subacute bacterial endocarditis.

WATER METABOLISM *

EDMUND ANDREWS, M.D.
CHICAGO

Investigators in the field of water metabolism have generally taken it for granted that all the water in the body is fixed by the colloids and electrolytes in a firm combination and that changes in this colloid-water complex must be postulated to account for any variations in the tissue fluid concentrations. Fischer,[1] indeed, postulated a "free" and "combined" water in the tissues, but the "free" water, according to his conception, seemed to be merely the superfluous fluid derived from metabolic processes or from ingestion which was promptly excreted.

During the course of studies of the so-called dehydration fevers in dogs it was noted that the diuresis produced by injections of equivalent amounts of glucose varied within wide limits and in many instances failed entirely.

These injections were made with the Woodyatt pump. Merck's "white granular glucose" was used. Balcar[2] injected 36 per cent. glucose solution at the rate of 15 gm. per kilogram of body weight per hour, using a carefully purified form of glucose. In my experiments such concentrations proved toxic, and a lower rate was adopted; 20 per cent. glucose solution was injected at the rate of 6 gm. per kilogram of body weight per hour. The injections were continued for ninety minutes. This may explain the failure of other observers to corroborate Woodyatt's results.

Detailed studies of the conditions of the dogs were made and many factors which might account for this variation were ruled out. The sugar metabolism, as shown by the amount of dextrose excreted and by blood sugar determinations before and during the experiments, varied within narrow limits. The parallelism of the rise in the blood sugar in different experiments showed that the glycogen reserve and the storage power were not factors.

The creatinin, nonprotein nitrogen, urea and cholesterol of the blood were studied together with the normal urinary findings as to albumin, casts, etc., and renal disease as a factor was ruled out.

It was noted, however, that the amount of water that it was possible to extract from the body by this means bore a definite relation to the

---

* From the department of experimental surgery, University of Illinois College of Medicine.

1. Fischer, M. F.: Edema and Nephritis, Ed. 3, London, John Wiley & Sons, 1921.

2. Balcar, J. O.; Sansum, W. D., and Woodyatt, R. T.: Fever and the Water Reserve of the Body, Arch. Int. Med. **24**:116 (July) 1919.

reaction of the tissues as measured by the plasma carbon dioxid combining power. This was determined by the Van Slyke method. The experiments given here are illustrative.

TABLE 1.—*Experiment 17*

A female dog, weighing 12.5 kg., was injected with 20 per cent. glucose solution at the rate of 6 gm. of glucose per kilogram of body weight per hour.

Time		Intake	Urine	Loss	Loss Per Kilogram
9:55	Injection begun, carbon dioxid combining power, 54				
10:10		90	75	...	..
10:25		181	180	...	..
10:40		273	350	77	6
10:55		365	520	155	12
11:10		456	800	344	27
11:25	Injection stopped	547	1,000	453	36
11:40		547	1,075	528	42
12:05		547	1,135	588	47
12:30	Urine ceased	547	1,175	628	51

TABLE 2.—*Experiment 18*

A female dog, weighing 8.5 kg., was injected with 20 per cent. glucose solution at the rate of 6 gm. of glucose per kilogram of body weight per hour.

Time		Intake	Urine	Loss	Loss Per Kilogram
10:00	Injection begun, carbon dioxid combining power, 46.5				
10:15		71	45	...	..
10:30		142	85	...	..
10:45		213	180	...	..
11:00		285	315	30	4
11:15		356	425	69	7
11:30	Injection stopped	427	475	50	6
11:45	Urine ceased	427	496	70	8

From a series of such experiments it was possible to construct Table 3.

TABLE 3.—*Results in Series of Experiments*

Experiment	Carbon Dioxid Combining Power	Loss Per Kilogram
12	44.5	0 (gained 50 c.c.)
19	45.5	13
13a	46.5	23
18	46.5	8
20	46.6	28
16	49.0	49
14	49.2	56
13	50.0	41
17	54.0	51 plus (some urine lost)

It will be seen from Table 3 that the critical point in the alkali reserve is about 45. Below that level it was not possible to produce any dehydration by the injection of glucose at this rate. As the alkali reserve rose there was a nearly parallel rise in the water loss. For each cubic centimeter of carbon dioxid, approximately 10 c.c. per kilogram of water is separable from the tissues.

COMMENT

It is not a new concept that water occurs in the tissues in different degrees of combination with the colloids. Fischer [1] postulated a "free" and a "combined" water. These terms are merely relative and probably represent a loose and a firm combination. Hitherto, it has been impossible to make any clear demonstration of this even in vitro, but the foregoing experiments not only afford a demonstration in vivo, but also a method of measuring the "free" water. For our purposes we may safely assume that the "combined" water cannot be freed by any such means used. The tenacity of the colloid-water compound is too great. The extent to which this method may be said to furnish a quantitative estimation of the "free" water is debatable, but in view of the accuracy with which small variations may be predicted, it is at least valuable as a relative measure when other factors are eliminated.

It is a reasonable deduction that the level of 45 of the carbon dioxid combining power is the point at which all the water in the body is "combined" or fixed. At least that is the level at which its affinity for the colloids in the tissues is greater than its affinity for the glucose. At higher levels there is in addition a certain amount of water in a looser combination, a water reserve.

This concept enables us to explain certain clinical phenomena which Fischer's reasoning will not.

It is well known that in suppression of urine from various causes the intravenous injection of Fischer's solution (sodium carbonate, 1.4 per cent.; sodium chlorid, 1 per cent.) will at times produce a flow of urine, but failure is perhaps more common. This can now be explained on the basis that the urinary flow will not be resumed until the carbon dioxid combining power is 45 or higher. The amount of alkali necessary to do this is tremendously in excess of that usually administered. Of course no amount of fluid given in extreme cases can be adequate because the degree of acidity of the tissues in severe acidosis may be sufficient to increase the hydrophilic action of the colloids to such an extent that the body would swell to twice its normal size if water were available. Illustrative experiments are given in Tables 4 to 6.

TABLE 4.—*Experiment 32*

Female dog, weighing 10 kg., given no food or water for thirty-six hours
9:20 a. m. Catheterized; heart blood taken; carbon dioxid combining power, 27.9
9:35 a. m. Urine only a few drops
9:35 a. m. Given 0.5 gm. of sodium bicarbonate (10 per cent. solution) intravenously
9:50 a. m. Urine only a few drops; heart blood taken; carbon dioxid combining power, 35

In Experiment 32 the amount of alkali administered was insufficient to raise the alkali reserve above the critical level and no diuresis ensued.

In Experiment 30 the alkali given was enough to raise the carbon dioxid combining power above 45 and prompt diuresis ensued.

Experiment 13 afforded a curious confirmation of this concept.

The dose of alkali administered in Experiment 13 was far too large and was rapidly fatal, but in the few minutes in which the dog survived 15 c.c. of urine was passed and the edema of the lungs was striking in its extent. After much had spilled on the floor, a beaker placed under the dog's head collected 50 c.c. of frothy mucus in a few minutes. The sudden overalkalinization of the tissues freed such a tremendous amount of fluid that there was no time to absorb it into the circulating mediums, and that part freed in the lungs found its way into the bronchi. This occurred in spite of the fact that the dog had already lost a maximal amount of water. This was repeated in subsequent experiments and it appears that if the amount of alkali necessary to

TABLE 5.—*Experiment 30*

Female dog, weighing 9 kg., given no food or water for forty-eight hours
2:30 p. m. Catheterized; heart blood taken; carbon dioxid combining power, 42
2:45 p. m. Only a few drops of urine
2:45 p. m. 0.5 gm. of sodium bicarbonate (10 per cent. solution) intravenously
3:00 p. m. 15 c.c. of urine; heart blood taken; carbon dioxid combining power, 47

TABLE 6.—*Experiment 13*

Female dog, weighing 10.4 kg., injected with 20 per cent. glucose solution at rate of 6 gm. per kilogram of body weight per hour for ninety minutes; animal lost 23 c.c. per kilogram. Flow of urine stopped in 95 minutes
Solution of 15 c.c. of 10 per cent. sodium bicarbonate injected into the right femoral vein
Animal died in six minutes from edema of the lungs; in these six minutes 15 c.c. of urine passed

bring an acid animal suddenly to the critical level is administered suddenly, edema of the lungs is the rule. In the cases in which there is not an undue amount of fluid held by the colloids, that is, in which the alkali reserve is already above the critical level, a much larger dose of alkali is easily tolerated.

BODY WEIGHT

According to the usual conceptions of the chemistry of colloids, the slightest variations in the reactions of the tissues should bring about changes in body weight. It is well known that this is not true clinically. There is a considerable range in which no such changes occur. That this range in the dog is that between the alkali reserve levels of 45 and 54 will be seen from the experiments in Tables 7 and 8.

In Experiment 21 the dog was near the critical level and the acid administered was sufficient to bring the carbon dioxid combining power well below it; water was retained, causing a gain in weight.

In Experiment 24 the critical level was not reached and no edema (gain in weight) occurred.

The buffer action of the water reserve is evident. The colloids must indeed attract water as the acidity increases, but within a moderate range; this water comes from the "free" portion and becomes fixed. Therefore human beings, as organisms, do not swell or shrink with slight changes in environment. The concentration of the blood as shown by refractometric methods decreased markedly in the first experiment but remained nearly the same in the second.

INTRADERMAL SALT SOLUTION TEST (ALDRICH [3])

During the course of these experiments numerous intradermal salt solution tests were made. Physiologic sodium chlorid solution, 0.2 c.c., was injected and the absorption time noted. By this method also it

TABLE 7.—*Experiment 21*

May 25, 1925	9:00 a. m.	Male dog, weighing 7.45 kg., received no food or water since 5 p. m. night before; carbon dioxid combining power of heart blood, 46.3; refractometer reading of plasma, 57
	9:15 a. m.	Usual food and drink restored
	3:00 p. m.	50 c.c. of 2 per cent. hydrochloric acid solution by stomach tube
	5:00 p. m.	All food and water taken away
May 26, 1925	9:15 a. m.	No food or water since 5:00 p. m. night before; weight 7.95 kg. (gain 0.5 kg.); carbon dioxid combining power, 27.3; refractometer reading of plasma, 50

TABLE 8.—*Experiment 24*

May 27, 1925	9:10 a. m.	Male dog, weighing 9.78 kg., received no food or water since 5 p. m. night before; carbon dioxid combining power, 53.7; refractometer reading, 56
	9:30 a. m.	Usual food and water restored
	3:00 p. m.	70 c.c. of 2 per cent. hydrochloric acid solution by stomach tube
	5:00 p. m.	All food and water taken away
May 28, 1925	9:00 a. m.	No food or water since 5 p. m. night before; weight 9.89 kg.; carbon dioxid combining power, 47; refractomer reading, 55

was possible to notice a critical level at which absorption became much more rapid. The difficulties of estimating just when absorption has taken place are considerable and the result would vary with different observers. However, it was clear that real tissue thirst did not begin until the carbon dioxid combining power level fell considerably under 45. Above this level the disappearance time was usually from twenty-five to forty minutes. When the alkali reserve was much below it, from

3. Aldrich, C. A., and McClure, W. B.: The Time Required for the Disappearance of Intradermally Injected Salt Solution, J. A. M. A. **82**:293-294 (July 28) 1923; Intradermal Salt Solution Test: Its Prognostic Value in "Nephritis" with Generalized Edema, J. A. M. A. **83**:1425-1428 (May 3) 1924. Aldrich, C. A.: The Clinical Course of Generalized Edema, with Suggestions as to Its Possible Function, J. A. M. A. **84**:481-486 (Feb. 14) 1925.

three to ten minutes was the rule. I was unable to set a more accurate critical point or to judge the results in intermediate cases on account of the difficulties of interpretation.

CONCLUSIONS

1. In dogs an amount of water varying from 0 to 72 c.c. per kilogram of body weight is held in a loose combination with the colloids, perhaps merely acting as a solvent for the colloids and electrolytes.

2. This water reserve in the dog is 0 at the level of 45 of the alkali reserve and rises about 10 c.c. for each cubic centimeter of the carbon dioxid combining power of plasma.

3. Certain hitherto inexplicable clinical phenomena may be explained on the basis that this water reserve is an active factor in water absorption and excretion.

Further studies are being undertaken to determine the effect of the hydrogen ion concentration on the "free" water; the effect of variations in the water reserve on blood pressure; intra-ocular tension; the use of salt solution dehydration as a measure of the water reserve, and the effect of variations in the water reserve on sugar and nitrogen metabolism.

GLUCOSE UTILIZATION IN RENAL GLYCOSURIA

JAMES E. PAULLIN, M.D.

ATLANTA, GA.

Renal glycosuria is ordinarily accepted as a condition in which the kidneys are abnormally permeable to glucose. There is usually a constant though not necessarily high excretion of sugar in the urine which is practically uninfluenced by diet. The blood sugar remains at a normal or subnormal level and the symptoms of diabetes mellitus, even in cases that have lasted over a period of years, do not appear. It has also been generally supposed that the body retains its power to utilize and store carbohydrate in a normal manner. The only evidence so far offered that the latter supposition is true is that of Finley and Rabinowitch [1] in a study of the gaseous metabolism of one case.

The present study gives the results of the administration of glucose on the respiratory quotient, total metabolism, blood sugar and glucose excretion in four cases of renal glycosuria. The technic employed in this investigation is that outlined by Boothby and Sandiford,[2] using a Tissot gasometer and Haldane gas analysis apparatus. Basal periods were first determined after a fast of approximately sixteen hours. Following the basal period blood was obtained for sugar estimation and the glucose then administered. In three of the cases 100 gm. was administered regardless of the weight; in the fourth case, 1.75 gm. per kilogram was given. Twenty minutes after the ingestion of the glucose the mask was adjusted for the first postglucose period. Other periods followed at half-hour intervals so that at least four observations were made following the glucose administration. At the end of each period blood was withdrawn for sugar estimation and urine was obtained for examination if possible.

The respiratory quotients used in apportioning the percentage of calories derived from carbohydrate and fat are not nonprotein quotients. It is realized that the determination of this would perhaps have made the experiments more accurate, yet one cannot be sure that the urinary nitrogen as determined during a short period of observation actually represents the protein destruction of this period. The suggestion of Voit [3] and others was adopted of deducting 15 per cent. of the calories

1. Finley, F. G., and Rabinowitch, I. M.: Renal Glycosuria, Quart. J. Med. **17**:260 (April) 1924. Since the preparation of this paper one other case has been studied by Ladd and Richardson (J. Biol. Chem. **63**:681 [April] 1925). This paper, like the others, reports a normal utilization of glucose in renal glycosuria.

2. Boothby, W. M., and Sandiford, I.: Laboratory Manual of the Technic of Basal Metabolic Rate Determination, Philadelphia, W. B. Saunders Company, 1920.

3. Voit, E.: Ztschr. f. Biol. **41**:188, 1901.

as representing the protein metabolized and proportioning the remainder to carbohydrate and fat according to the table of Zuntz and Schumburg as modified by Lusk.[4]

REPORT OF CASE

CASE 1.—P. D., a white man, aged 32, height 173 cm., weight 50 kg., was first observed in 1916. He had had a constant glycosuria uninfluenced by diet for the last nine years. During a period when first observed there was dietary regulation which did not influence the glycosuria. Since that time there had been no dietary regulation; he had remained in excellent health with no symptoms of diabetes mellitus. He was given, under the experimental conditions stated above, 100 gm. of glucose. Table 1 shows the results.

TABLE 1.—*Results in Case 1*

	Respiratory Quotient	Calories per Hour	Rise in Calories per Hour	Calories per Square Meter per Hour	Rise Above Normal, per Cent.	Calories from Carbohydrate and Fat	Calories from Carbohydrate per Cent.	Calories from Carbohydrate	Grams Carbohydrate Utilized: Total	Grams Carbohydrate Utilized: Increase	Blood Sugar, Mg. per 100 C.c.	Urine Sugar, Gm.
Basal.....	0.79	59.9	...	37.7	—5	51.0	29.9	15.9	3.9	...	70	0.161
½ hour after 100 gm. glucose....	0.90	67.1	7.2	42.2	7	57.1	67.5	38.5	9.6	5.7	150	0.380
1 hour after	0.92	65.9	6.0	41.4	5	57.0	74.1	42.2	10.5	6.6	170	0.500
1½ hours...	0.83	61.9	2.0	38.9	—1	52.6	43.8	23.0	5.6	1.7	90	0.581
2½ hours...	0.89	57.6	—2.3	36.2	—7	48.9	64.2	31.4	7.8	3.9	85	0.571

Glucose administered ..... 100.0 gm.
Glucose excreted ..... 2.2 gm.
97.8 gm.

Glucose metabolized, 16.7 gm., 17 per cent. of total.

CASE 2.—G. W., a white man, aged 39, height 180 cm., weight 59.1 kg., had glycosuria discovered during an insurance examination in 1909. Since that date there had been a more or less constant glycosuria with occasional periods when urinary specimens would be sugar-free. For many months at a time the sugar was constantly present in the urine. There had been no dietary control and no symptoms of diabetes. He had previously had three glucose tolerance tests, all with normal curves except one. The abnormal curve was obtained after the patient had been steadily and heavily using alcohol internally for several days. He was given 100 gm. of glucose with the results given in Table 2.

CASE 3.—P. M., a white man, aged 32, weight 74.6 kg., height 186 cm., had glycosuria discovered during an insurance examination in 1915. No further urinalyses were made until 1923, when during an insurance examination sugar was again detected. The glycosuria disappeared with a marked restriction of carbohydrate. During the last eighteen months he had had many urinalyses; sugar had been found in each specimen examined, but there were no symptoms of diabetes. He was given 100 gm. of glucose; Table 3 shows the results.

CASE 4.—Mrs. F., a white woman, aged 21, weight 47.3 kg., height 157.5 cm., had sugar discovered in the urine during 1922; at this time she was pregnant. Pregnancy was normal and without dietary control; she bore a perfectly healthy child. In July, 1923, she had typhoid fever, hemorrhages and relapse. Every specimen of urine examined since glycosuria was first discovered had shown the presence of sugar. She had never had any symptoms of diabetes. At the time of this observation she was three weeks pregnant, had some nausea and on this account had been on a quite restricted diet. She was given 79 gm. of glucose; Table 4 shows the results.

4. Lusk, G.: J. Biol. Chem. **59**:41 (Feb.) 1924.

TABLE 2.—*Results in Case 2*

	Respiratory Quotient	Calories per Hour	Rise in Calories per Hour	Calories per Square Meter per Hour	Rise Above Normal, per Cent.	Calories from Carbohydrate and Fat	Calories from Carbohydrate per Cent.	Calories from Carbohydrate	Grams Carbohydrate Utilized: Total	Grams Carbohydrate Utilized: Increase	Blood Sugar, Mg. per 100 C.c.	Urine Sugar, Gm.
Basal.....	0.74	68.5	...	39.6	+1.0	58.2	12.0	7.0	1.7	...	79	....
½ hour after 100 gm.	0.82	71.0	2.5	42.0	7.0	60.3	40.3	24.3	6.0	4.3	150	0.80
1 hour after	0.85	77.5	9.0	44.8	14.0	65.8	50.7	33.4	8.3	6.6	130	0.90
1½ hours...	0.84	74.3	5.8	42.9	9.0	63.1	47.2	29.8	7.4	5.7	98	0.30
2 hrs. after	0.86	73.1	4.6	42.2	7.0	62.1	54.1	33.6	8.4	6.7	105	0.36

Glucose administered	100.0 gm.
Glucose excreted	2.4 gm.
	97.6 gm.

Glucose metabolized, 15.5 gm., 15.9 per cent. of total.

TABLE 3.—*Results in Case 3*

	Respiratory Quotient	Calories per Hour	Rise in Calories per Hour	Calories per Square Meter per Hour	Rise Above Normal, per Cent.	Calories from Carbohydrate and Fat	Calories from Carbohydrate per Cent.	Calories from Carbohydrate	Grams Carbohydrate Utilized: Total	Grams Carbohydrate Utilized: Increase	Blood Sugar, Mg. per 100 C.c.	Urine Sugar, Gm.
Basal.....	0.71	66.9	....	34.3	—13	56.8	1.10	6.24	1.5	...	80	.....
½ hour after 100 gm. glucose....	0.80	80.9	14.0	41.5	+5.5	68.7	33.4	23.0	5.7	4.2	84	0.400
1 hour after	0.81	82.5	15.6	42.3	7	70.1	36.9	25.9	6.5	5.0	86	0.500
1½ hours...	0.88	86.2	19.3	44.2	12	73.2	60.8	44.5	11.1	9.6	86	0.500
2 hrs. after	0.88	92.1	25.2	47.3	19	78.3	60.8	47.6	11.9	10.4	100	0.300

Glucose administered	100.0 gm.
Glucose excreted	1.7 gm.
	98.3 gm.

Glucose metabolized, 17.6 gm., 18.9 per cent. of total.

TABLE 4.—*Results in Case 4*

	Respiratory Quotient	Calories per Hour	Rise in Calories per Hour	Calories per Square Meter per Hour	Rise Above Normal, per Cent.	Calories from Carbohydrate and Fat	Calories from Carbohydrate per Cent.	Calories from Carbohydrate	Grams Carbohydrate Utilized: Total	Grams Carbohydrate Utilized: Increase	Blood Sugar, Mg. per 100 C.c.	Urine Sugar, Gm.
Basal.....	0.78	55.4	....	37.9	—2	47.1	26.3	12.3	3.0	....	78	+
79 gm. glucose 45 minutes after.....	0.87	62.2	6.8	42.6	16.5	52.8	57.5	30.3	7.6	4.6	133	3.5
1½ hours...	0.78	59.7	4.3	40.9	11.0	50.7	26.3	13.4	3.3	.3	132	2.0
2½ hours...	0.76	56	0.6	38.4	3.5	47.6	19.2	9.2	2.3	—.7	100	1.5

Glucose administration	79.0 gm.
Glucose excreted	7.0 gm.
	72.0 gm.

Glucose metabolized, 10.5 gm., 14.6 per cent. of total.

From the accompanying tables it is evident that within one-half hour following the administration of a large dose of glucose there is a noticeable rise in the respiratory quotient, which reaches its highest level from one to one and one-half hours after the ingestion of the glucose. With this rise in the quotient there also is an increase in the basal metabolic rate, from 7 to 19 per cent. above normal. A corresponding increase in the calories derived from carbohydrate is evidenced by the tables. The amount of glucose utilized in these cases varied from 14.6 to 18.9 per cent. of that ingested, an average of 16.6 per cent. for all.

It has previously been shown by Higgins,[5] Benedict and Carpenter,[6] Sanger and Hun,[7] McCann and Hannon[8] and others, that the normal person, following the ingestion of glucose, responds with a rise in the respiratory quotient within half an hour, although in rare instances there may be a primary fall. However, after one hour the quotient in all cases rises rapidly and approaches 1, which is the respiratory quotient when carbohydrate only is oxidized. There also is an increase in the basal rate from normal to 10 or 20 per cent. above normal.

COMMENT

It would seem, therefore, that patients with renal glycosuria metabolize and store carbohydrate in the same way as normal persons. The previous supposition, viz., that patients with renal glycosuria metabolize carbohydrate in a normal way is justified, and so far as the evidence points they do not develop diabetes mellitus.

---

5. Higgins, H. L.: The Rapidity with Which Alcohol and Some Sugars May Serve as Nutriment, Am. J. Physiol. **41**:258 (Aug.) 1916.

6. Benedict, F. G., and Carpenter, T. M.: Food Ingestion and Energy Transformations, Pub. 261 Carnegie Institute of Washington, pp. 206-208.

7. Sanger, B. J., and Hun, E. G.: Glucose Mobilization Rate in Hyperthyroidism, Arch. Int. Med. **30**:396 (Sept.) 1922.

8. McCann, W. D., and Hannon, R. R.: Studies of Diabetes Mellitus, Bull. Johns Hopkins Hosp. **34**:73 (March) 1923.

THE PHYSIOLOGY OF SYNOVIAL FLUID*

F. A. CAJORI, PH.D.
C. Y. CROUTER, M.S.
AND
RALPH PEMBERTON, M.D.
PHILADELPHIA

Little is known concerning the origin and functions of the synovial fluid which has not been the subject of extensive chemical investigation. It is more or less evident that the synovial fluid plays a lubricating rôle in joint structures by virtue of its content of mucin, but to what extent, if at all, it serves as a nutritive medium is not clearly established. In view of the fact that articular cartilage has a small blood supply, the synovial fluid has been regarded as aiding in its growth and nutrition. William Hunter first demonstrated in connection with articular cartilage the existence of the circulus articuli vasculosus but this system supplies only the lateral aspects, leaving the bulk of articular cartilage without direct blood supply. Gray [1] refers to articular cartilage as a nonvascular structure.

More than eighty years ago, Toynbee advanced the view that articular cartilage derives its chief pabulum from the plasma exuded by the capillary loops below the subarticular layers of bone. More recently, Strangeways [2] has again drawn attention to the synovial fluid as a source of nutriment on the basis of the growth observed in fragments of the articular surface which sometimes become loose in the joint.

In a recent series of interesting studies, Fisher [3] has reached the opinion that there is an element of truth in each of these views. Using injection methods he has found the subarticular region to be freely permeable and concludes that "it is probable that nutrient plasma is also able to permeate this zone and nourish the deeper layer of the cartilage." Fisher further stresses the recognized anatomic fact that the central articular area of cartilage is removed from contact with either the laterally placed blood vessels or the deeper subarticular tissues and believes that there is a fundamental difference between the structure and nutrition of the central and the lateral regions respectively. In an effort to determine the degree to which the central area may obtain its nutrition through the synovial fluid he has determined the total solids, the protein content and mucin in the supposedly normal synovial fluid of human beings and oxen, and in the lymph plasma of human beings. He found "a somewhat low protein content" but believes, in spite of this fact, that the synovial fluid nourishes the superficial cells of the central articular area. The actual capacity of the synovial fluid to do this was left undetermined.

---

* From the laboratory of clinical chemistry, Presbyterian Hospital. The work here reported is part of a study on chronic arthritis in collaboration with Dr. Robert B. Osgood of Boston. The expenses were defrayed by contributions from several sources, including a number of patients.

* Presented before the Pathological Society, Philadelphia, March 19, 1925.

1. Gray, Henry: Anatomy, Ed. 22, London, 1923.
2. Strangeways, T. S. P.: Brit. M. J. **1**:661 (May 15) 1920.
3. Fisher, A. G. T.: Lancet **2**:514 (Sept. 15) 1923.

Fisher's morphologic studies indicate to him that the synovial membrane differs markedly in its structure at different sites in the same articulation. Near the articular margins, however, there are oval or round connective tissue cells whose function appears to be the secretion of the synovia, including mucin, which he regards as a pure lubricant. The name synovial gland was given to these cells by Havers and it has been suggested that the pressure resulting from the joint movements contributes to expression of their contents into the joint cavity. Fisher also states that the synovial membrane allows the transudation, from the plexus of capillaries, with which it is supplied, of the albuminous fluid that, in his opinion, nourishes the central superficial area of the articular cartilage.

According to Piersol[4] it is certain that absorption takes place from joints, presumably through the well developed lymphatics found beneath the inner surface of the synovial membrane, but no direct openings into the articular cavity have been demonstrated. Fisher has demonstrated the absorption of potassium iodid, Berlin blue and colloidal silver.

The contact of the internal joint structures with the blood is therefore largely indirect and it is important to ascertain the degree to which the nutritive and other constituents of the blood influence the composition of the synovial fluid. This information is desirable on the physiologic grounds mentioned but also because of its possible bearing on the disease processes affecting cartilage and the associated joint structures in various forms of arthritis. The observations reported here were carried out with the aim of throwing light on some phases of the subject. The problem has been approached, experimentally, in two ways:

1. Certain features of the chemical composition of synovial fluid, as obtained from cases of joint effusion, have been determined and compared with those of blood plasma. Most of the chemical data hitherto available represent work, largely German, carried out before the advent of micro methods, the application of which during the last decade has aided in a quantitative way toward a solution of many physiologic and pathologic problems.

2. In order to study more directly the influence of the blood on the composition of synovial fluid, changes in the concentration of certain constituents of blood have been experimentally produced and the effect of such changes on the composition of joint fluid has been determined.

EXPERIMENTAL WORK

The synovial fluid was obtained by passing a spinal fluid or Wassermann needle into the joint cavity and withdrawing the fluid, under mineral oil, into a syringe. Procain was usually used to anesthetize the site of the puncture. In experiments involving removal of fluid in more than one stage, either a second puncture was made or the needle was allowed to remain in the joint cavity and was held immobile by suitable bandaging.

4. Piersol, G. A.: Human Anatomy, Ed. 6, Philadelphia, 1918.

TABLE 1.—*Composition of Nonpurulent Synovial Fluid*

Experiment	Date	Site	p_H	Total Carbon Dioxid Content, Percentage by Volume	Sugar, Mg. per 100 C.c.	Lactic Acid, Mg. per 100 C.c.	Nonprotein Nitrogen, Mg. per 100 C.c.	Uric Acid, Mg. per 100 C.c.	Ash, per Cent.	Sodium Chlorid, Mg. per 100 C.c.	Calcium, Mg. per 100 C.c.	Viscosity, 20 Degrees	Total Solids, per Cent.	Total Nitrogen, per Cent.	Total Protein, per Cent.
Normal values whole blood.....			7.3-7.5*	52-61†	77-116†	14-25‡	28-39†	3.0-5.0§	....	450-500‖	.....	.....	.....	.....	.....
Normal values plasma.....			7.3-7.5*	60-71†	77-114†	.....	18-30†	.....	0.85	570-620‖	9-11‖	1.7-2.0†	8.5-9.8†	1.20-1.43†	7.3-8.7†
1	11/ 2/20	Left knee	....	57.9	73	..	..	...	....	...	....	....	....	....	....
2	11/ 2/20	Right knee	....	55.2	68	..	..	...	....	...	....	....	....	.....	.....
3	12/ 8/20	Left knee	....	68.1	132	..	..	...	....	...	....	....	....	1.16	7.25
4	12/ 8/20	Right knee	....	62.5	96	..	..	...	....	...	....	....	....	0.83	5.19
5	5/24/21	Left knee	....	63.9	100	..	..	...	....	...	....	....	....	1.06	6.63
6	4/25/22	Left knee	.....	68.0	120	..	..	...	....	...	....	....	....	0.96	6.00
7	3/16/23	.....	7.35	54.2	110	..	43	4.7	....	...	....	....	....	....	....
8	2/ 8/24	.....	6.99	43.1	69	28	..	3.4	0.79	....	....	....	6.34	....	....
9	11/14/24	.....	7.36	47.0	87	..	..	4.0	1.10	409	....	....	7.50	....	....
10	12/19/24	Left knee	7.32	54.6	90	..	25	...	0.96	568	10.7	7.6	6.13	0.93	5.65
11	11/21/24	Left knee	7.45	62.0	82	13	36	4.3	0.80	513	10.0	11.8	7.62	....	....
12	12/11/24	Left knee	7.43	56.8	86	..	..	...	....	....	....	16.7	....	....	....
13	1/11/25	Left knee	7.45	56.4	..	..	30	...	....	445	....	8.3	7.45	0.86	5.19
14	5/18/25	Left knee	7.47	59.3	...	..	41	3.3	....	633	....	11.8	....	0.82	4.87
15¶	4/14/25	Right knee	7.58	55.2	....	..	40	3.5	....	...	....	3.3	6.25	0.71	4.18
16	4/27/25	Left knee	7.51	49.3	110	..	31	3.6	0.76	624	8.3	3.4	6.44	0.74	4.40
17	5/ 8/25	Left knee	....	....	...	..	24	4.4	....	617	....	2.7	6.39	0.77	4.68
18	6/ 3/25	Left knee	7.42	57.5	105	..	22	...	....	619	....	2.7	6.03	0.79	4.79

* Van Slyke, D. D.: J. Biol. Chem. **48**: 153 (Sept.) 1921.
† Gram, H. C.: Am. J. M. Sc. **168**: 511 (Oct.) 1924.
‡ Barr, D. P.; Himwich, H. E., and Green, R. P.: J. Biol. Chem. **55**: 495 (March) 1923.
§ Lennox, W. G., and O'Conner, M. F.: J. Lab. & Clin. Med. **10**: 99 (Nov.) 1924.
‖ Myers, V. C.: Practical Chemical Analysis of Blood, Ed. 2, C. V. Mosby Company, 1924.
¶ Effusion result of trauma: fluid bloody; oxygen capacity 6.1 per cent. by volume.

With one exception, the subjects were patients with arthritis who showed joint effusion. It was difficult or impossible to classify them into morphologic types, such as proliferative and degenerative, but two of the subjects (Subjects P and K) represented intermittent hydrarthrosis, one very typically. The knee was the joint examined in all cases.

The synovial fluid from these cases was light yellow, slightly turbid and nonpurulent. Patient 15 was a normal person with an effusion resulting from trauma and this fluid was highly colored and contained much old blood.

In Table 1 are presented the results of analyses of eighteen synovial fluids. Included in this table, for the sake of comparison, is the range of concentration of each constituent in normal blood and blood plasma.

The following analytic methods were used for blood and synovial fluid. The hydrogen ion concentration was determined by Cullen's colorimetric method [5] or Hawkin's modification of this method; [6] the carbon dioxid by the method and apparatus of Van Slyke and Stadie.[7] Folin's methods were used for the determination of nonprotein nitrogen and glucose.[8] Uric acid was determined by Benedict's method,[9] lactic acid by Clausen's,[10] sodium chlorid by Whitehorn's method [11] and calcium by the method of Kramer and Tisdall.[12] Total nitrogen was determined by a Kjeldahl method and the total protein calculated from the total nitrogen by multiplying by the factor 6.25. When the nonprotein nitrogen had also been determined this was subtracted from the total nitrogen before calculating the protein. Viscosity was measured with a Hess viscosimeter and the results were corrected to 20 degrees. The total solids and ash were determined in the usual way.

With few exceptions, the diffusible constituents, carbon dioxid, sugar, lactic acid, uric acid, nonprotein nitrogen, sodium chlorid and calcium were present in synovial fluid in concentrations that are close to the concentrations of the same constituents in normal blood. Fasting arthritic blood has not been shown to diverge from normal in respect to these constituents.

Boots and Cullen [13] studied the p_H of synovial exudates of patients with rheumatic fever and chronic arthritis and found a p_H range of 7.33

5. Cullen, G. E.: J. Biol. Chem. **52**:501 (June) 1922.
6. Hawkins, J. A.: J. Biol. Chem. **57**:493 (Sept.) 1923.
7. Van Slyke, D. D., and Stadie, W. C.: J. Biol. Chem. **49**:1 (Nov.) 1921.
8. Folin, O.: Laboratory Manual of Biological Chemistry, Ed. 3, New York, D. Appleton & Co., 1922, pp. 235, 253.
9. Benedict, S. R.: J. Biol. Chem. **51**:187 (March) 1922.
10. Clausen, S. W.: J. Biol. Chem. **53**:263 (May) 1922.
11. Whitehorn, J. C.: J. Biol. Chem. **45**:449 (Feb.) 1921.
12. Kramer, B., and Tisdall, F. F.: J. Biol. Chem. **46**:339 (April) 1921.
13. Boots, R. H., and Cullen, G. E.: J. Exper. Med. **36**:405 (Oct.) 1922.

to 7.47 in sterile fluid. Fluid from septic joints was more acid, p_H 6.19 and 6.69. In agreement with these authors, the p_H values obtained in the present series, with two exceptions, are within the range of normal blood p_H. There was no evidence of an infected joint in Patient 8, whose joint fluid was p_H 6.99. The carbon dioxid content of this fluid also was low. A rather alkaline reaction, p_H 7.58, was found in the bloody fluid from the patient with knee injury.

The carbon dioxid content of synovial fluid, as revealed by these figures, is in some cases slightly below the range of carbon dioxid content of venous blood plasma. The carbon dioxid figures are not low, however, if the fluid is considered as being in equilibrium with arterial blood.

A few cases of synovial fluid with low sugar content were found, though in general the sugar content is within the range of blood sugar. The fact that the synovial fluid has a content of sugar as high as that of blood is of interest and is an argument in favor of the view that its function is partly nutritional. It is not generally appreciated that cartilage contains considerable amounts of glycogen. Carbohydrate is presumably necessary for replacement and maintenance of glycogen stores, and provision of carbohydrate appears to be relatively more important than provision of nitrogen. Cartilaginous bodies, loose in the joint cavity and growing, find in synovial fluid ample pabulum.

There is no indication, from two observations, that lactic acid is present in synovial fluid in amounts greater than in circulating blood.

The nonprotein nitrogen and uric acid figures give no evidence of accumulation of nitrogenous end products in joints and lend no support to hypotheses that ascribe to uric acid a causative rôle in arthritis.

Since the nonprotein nitrogen content of synovial fluid is comparable to that of blood, it may be inferred that its amino-acid content is likewise similar to that of blood. The amino-acids are the source from which the materials necessary for nitrogenous metabolism may be derived rather than the protein content, as stated by Fisher.

Values for sodium chlorid lower than normal plasma values were found in some synovial fluids, though the ash content and calcium content are not far from what have been observed in blood plasma.

The similarity of chemical composition of synovial fluid and blood plasma does not extend to the nondiffusible constituents. As is seen in Table 1, arthritic synovial fluid is low in total solids and total protein when compared with blood plasma. As already mentioned, Fisher has also found a low protein content in synovial fluids obtained postmortem from normal (?) joints. Despite its low protein content, the viscosity of synovial fluid is high, in some cases from four to five times greater

than that of plasma. Salkowski [14] and later Von Holst [15] isolated from synovial fluid mucin-like proteins, serosamucins as Von Holst termed them.

In view of the low protein content of synovial fluid, the "sticky" nature and high viscosity suggest that its particular characteristics, distinctive from blood and plasma, are due to the contained mucin.

Experiments were carried out in which the blood and synovial fluid were analyzed before and after giving 100 gm. of glucose by mouth. The results of four such experiments, which are given in Table 2, reveal a communion of the synovial fluid with the alimentary tract that is novel

TABLE 2.—*Effect of Ingestion of Glucose on the Composition of Synovial Fluid and of Venous Blood*

Sample	Time, A. M.	Sugar, Mg. per 100 C.c.	Viscosity, 20 Degrees	Total Solids, per Cent.	Uric Acid, Mg. per 100 C.c.	Sodium Chlorid, Mg. per 100 C.c.	Total Nitrogen, per Cent.
Experiment 1, Subject K, Nov. 21, 1924							
Blood 1	10:10	86	....	....	4.3	409	....
Synovial fluid 1	10:15	82	11.8	7.62	4.3	513	....
100 gm. glucose by mouth.	10:20	...	....	....	...	...	....
Blood 2	10:55	167	....	....	4.5	367	....
Synovial fluid 2	11:05	171	8.1	7.20	4.4	546	....
Blood 3	11:25	153	....	....	4.6	399	....
Synovial fluid 3	11:35	171	4.9	6.16	4.4	566	....
Experiment 2, Subject K, May 18, 1925							
Blood 1	11:50	95	....	....	...	...	....
100 gm. glucose by mouth.	11:58	...	....	....	...	...	....
Blood 2	12:40	142	....	....	...	...	....
Synovial fluid 1	12:35	160	11.8	....	...	...	....
Blood 3	1:25	128	....	....	...	...	....
Synovial fluid 2	1:20	163	9.6	....	...	...	....
Experiment 3, Subject C, May 8, 1925							
100 gm. glucose by mouth.	9:15	...	....	....	...	...	....
Blood 1	10:05	116	....	....	4.4	...	....
Synovial fluid 1	10:05	135	2.7	6.39	4.4	617	....
Blood 2	11:05	80	....	....	4.1	493	....
Experiment 4, Subject P, Dec. 19, 1924							
Blood 1	9:35	99	....	....	...	...	....
Synovial fluid 1	10:15	90	7.6	6.13	...	...	0.93
100 gm. glucose by mouth*	10:20-30	...	....	....	...	...	....
Blood 2	11:20	125	....	....	...	...	....
Synovial fluid 2	11:05	101	7.0	6.15	...	...	0.88

* Subject nauseated; only three fourths of sugar dose consumed.

and not heretofore suspected. The rise in blood sugar following glucose ingestion promptly causes a rise in sugar concentration within the joint with no evidence of a lag. In Experiments 2 and 3 the concentration of sugar in the synovial fluid, half an hour and one hour after the taking of the sugar, was higher than the concentration of sugar in the blood at these times. This may mean that there is a tendency for sugar to accumulate in the joint cavity, though it seems more likely that it represents an equilibrim with respect to sugar between arterial blood and synovial

14. Salkowski, E.: Virchows Arch. f. path. Anat. **131**:304, 1893.
15. Von Holst, G.: Ztschr. f. physiol. Chem. **43**:145, 1904-1905.

fluid. The analyses were made on venous blood, which usually has a much lower sugar content, following sugar ingestion, than has arterial blood. Experiment 4 was the least successful of those conducted. The subject was extremely nauseated as a result of the joint puncture and dose of sugar, being unable to consume all of the sugar solution. In this case, fifteen minutes elapsed between the second venous puncture and the second joint puncture, a lapse of time during which the level of circulating sugar may have materially changed.

It will be seen that the viscosity of the synovial fluid became progressively lower as samples were removed from the joint. A fall in viscosity has usually been observed when the joint is tapped in successive stages with a suitable time interval between punctures. This indicates a dilution of the fluid remaining in the joint cavity with a more watery liquid.

TABLE 3.—*Effect of Ingestion of Sodium Bicarbonate on the Composition of Synovial Fluid and Blood*

Sample	Time, P. M.	Total Carbon Dioxid, per Cent. by Volume	Carbon Dioxid Capacity, per Cent. by Volume	p_H	Viscosity, 20 Degrees	Solids, per Cent.
Experiment 1, Subject K, Jan. 11, 1925						
Blood 1*	12:50	50.7	....	7.45	....	....
Synovial fluid 1	12:55	56.4	....	7.45	7.5	7.36
10 gm. sodium bicarbonate by mouth	1:03	....	....	....	....	....
Blood 2	1:39	59.6	....	7.53	....	....
Synovial fluid 2	1:45	61.0	....	7.45	7.1	7.08
Experiment 2, Subject K, May 18, 1925						
Blood 1†	12:40	55.4	63.8	7.42	....	....
Synovial fluid 1	12:35	59.3	....	7.47	11.8	....
10 gm. sodium bicarbonate by mouth	12:45	....	....	....	....	....
Blood 2	1:23	62.2	64.7	7.40	....	....
Synovial fluid 2	1:20	59.9	....	7.47	9.6	....

* Four minutes after electric "bake."
† Forty-two minutes after sugar ingestion.

The entry of sugar into the joint is not, however, to be ascribed merely to refilling of the partly emptied cavity with a sugar-rich fluid from the blood. In Experiments 2 and 3, the initial tapping of the joint was purposely delayed until after the sugar had been administered. The fasting level of synovial fluid sugar in the subjects of these experiments had previously been determined. A prompt rise of sugar in the synovial fluid was observed under these conditions, precisely as had been observed when the joint cavity was partly emptied and refilling was taking place.

The ease with which glucose can gain access to the joint cavity gives definite basis to the view that regards synovial fluid as a pabulum from which the tissues bathed by it, especially the central area of the articular cartilage, may derive their nutrient requirements. This fact obviously suggests that other diffusible substances may behave likewise.

The possibility of entry of harmful as well as nutritive substances is further suggested and emphasizes the necessity of regarding the gastrointestinal tract as a source of possibly undue amounts of normal products of digestion as well as toxic material.

Two experiments were carried out in which a solution containing 10 gm. of sodium bicarbonate was given each of two subjects and the effect on the blood and synovial fluid observed. Collip and Bakus [16] report a lag in changes in alkali reserve in spinal fluid when such changes are induced in the blood by bicarbonate feeding. The results of the present experiments are given in Table 3. In both cases a rise in carbon dioxid content of blood followed the ingestion of bicarbonate. In Experiment 1 the carbon dioxid content of the blood rose 8.9 per cent. by volume and in the same time the carbon dioxid content of the synovial fluid rose 4.6 per cent. by volume. In the second experiment no increase in carbon dioxid content of the synovial fluid was observed, though the blood carbon dioxid increased 7 per cent. by volume. There was no increase in the carbon dioxid capacity of this blood, however, in spite of the bicarbonate feeding.

It has previously been shown by us [17] that the blood of a subject exposed to external heat in an electric cabinet during a forty minute "bake" may become more alkaline as a result of loss of carbon dioxid. In order to determine whether the contact of the synovial fluid with the blood is sufficiently intimate to induce similar changes in the synovial fluid, the p_H and carbon dioxid content of the blood and the synovial fluid of patients with joint effusion were determined before and after exposure to external heat. This consisted, as in the previous studies, in a thirty to forty minute "bake" in an electric baker.

Five experiments of this kind were carried out and the results are given in Table 4. An alkaline swing in the blood, of sufficient magnitude to be significant, was induced in only two of the experiments (Experiments 1 and 4). In these two cases there was no change in the p_H of the synovial fluid or in its carbon dioxid content despite the changes that occurred in the blood. It is difficult to interpret these results. The conclusion that gas exchange between blood and synovial fluid does not take place freely is perhaps not justified. Such a conclusion would not harmonize well with the clear cut experiments showing the passage of glucose from blood to synovial fluid. Little is known of the base binding capacity of the proteins peculiar to synovial fluid and the ability of such a buffered fluid to resist changes in reaction. Further, in these experiments, the p_H was determined in all cases by Cullen's colorimetric method,

16. Collip, J. B., and Bakus, P. L.: Am. J. Physiol. **51**:551 (April) 1920.

17. Cajori, F. A.; Crouter, C. Y., and Pemberton, R.: J. Biol. Chem. **57**:217 (Aug.) 1923.

which involves a large empirical correction. It has recently been shown [18] that this correction is not a constant and may vary widely in blood in which the protein content is altered as after hemorrhage. It may be that in the experiments here reported, p_H changes are masked, when determined colorimetrically. Further work will be carried out in an endeavor to clarify this phase of the subject.

TABLE 4.—*Effect of Exposure to External Heat on Composition of Synovial Fluid and Venous Blood*

Sample	Time, A. M.	Body Temperature, F.	p_H	Total Carbon Dioxid, per Cent. by Volume	Viscosity, 20 Degrees	Solids, per Cent.	Uric Acid, Mg. per 100 C.c.
Experiment 1, Subject D, Feb. 8, 1924							
Blood 1	10:00	....	7.30	....	....	....	...
Synovial fluid 1	10:25	....	6.99	43.1	....	6.34	3.4
Electric "bake" began	10:40	98.6	....	....	....	....	...
ended	11:25	100.0	....	....	....	....	...
Blood 2	11:30	....	7.43	51.1	....	....	...
Synovial fluid 2	11:30	....	6.96	44.5	....	6.76	3.3
Experiment 2, Subject M, Nov. 14, 1924							
Blood 1	9:30	....	7.41	49.4	....	....	3.8
Synovial fluid 1	10:10	....	7.36	47.0	....	7.50	4.0
Electric "bake" began	10:20	....	....	....	....	....	...
ended	10:50	99.2	....	....	....	....	...
Blood 2	11:00	....	7.44	49.9	....	....	3.8
Synovial fluid 2*	11:25	....	7.36	48.4	....	7.49	4.5
Experiment 3, Subject K, Dec. 11, 1924							
Blood 1	11:14	....	7.41	54.0	....	....	...
Synovial fluid 1	11:30	....	7.43	56.8	16.7	....	...
Electric "bake" began	11:42	....	....	....	....	....	...
ended	12:15	99.4	....	....	....	....	...
Blood 2	12:25	....	7.43	53.2	....	....	...
Synovial fluid 2	12:35	....	7.43	55.0	12.3	....	...
Experiment 4, Subject K, Jan. 11, 1925							
Blood 1	12:00	....	7.37	53.6	....	....	...
Synovial fluid 1	11:50	....	7.45	56.4	8.3	7.45	...
Electric "bake" began	12:06	98.2	....	....	....	....	...
ended	12:44	99.6	....	....	....	....	...
Blood 2	12:50	....	7.45	50.7	....	....	...
Synovial fluid 2	12:55	....	7.46	56.4	7.5	7.36	...
Experiment 5, Subject C, June 3, 1925							
Blood 1	9:45	....	7.42	53.3	....	....	...
Synovial fluid 1	10:15	....	7.42	57.5	2.7	6.03	...
Electric "bake" began	10:30	98.3	....	....	....	....	...
ended	11:05	99.4	....	....	....	....	...
Blood 2	11:07	....	7.42	54.8	....	....	...
Synovial fluid 2	11:07	....	7.46	57.6	3.1	6.35	...

* Fluid removed with difficulty and much pain.

SUMMARY

The concentration of certain of the chemical constituents of nonpurulent synovial fluid from arthritic patients with joint effusion has been determined.

Changes in the composition of the blood have been induced experimentally by glucose feeding, administration of sodium bicarbonate and

18. Bennet, Mary A.: Personal communication to the authors.

exposure to external heat. The effect of such blood changes on the composition of synovial fluid has been observed.

The concentration of the diffusible constituents of synovial fluid, uninfluenced by experimental feeding, closely approaches that of blood plasma. It has been found that, following glucose ingestion, the sugar concentration of synovial fluid promptly rises to a level as high as, or higher than, that in venous blood.

It is concluded from such experiments that diffusible substances pass easily from the blood to the synovial fluid and that the gastrointestinal tract must be regarded as being in surprisingly close communion with the joint fluids. The possibility of detriment from this source is pointed out.

The adequacy of the synovial fluid for the nutrition of cartilage from the standpoint of carbohydrate and energy yielding content is clearly indicated.

Experiments involving changes in the acid-base equilibrium of the blood have not shown corresponding changes in the synovial fluid. Further work will be necessary before these results can be satisfactorily explained.

BLOOD SUGAR CURVES IN EPIDEMIC ENCEPHALITIS *

J. KASANIN, M.D.
AND
G. P. GRABFIELD, M.D.
BOSTON

The increase in the sugar content of the spinal fluid in epidemic encephalitis led us to investigate the sugar metabolism of patients suffering from this disease by means of the blood sugar curve. This method of studying the sugar metabolism has been criticized by a number of observers. Fitz's [1] careful studies have shown that all the ingested glucose may not be absorbed, and Rowe [2] has abandoned the glucose curve in his studies of endocrinopathies. However, Gray [3] from an analysis of 4,000 curves was able to define the limits of variation of the blood sugar after the ingestion of glucose with sufficient accuracy to indicate that information about the sugar metabolism may be obtained by this method.

Alexander [4] states that the sugar curve in encephalitis tends to be higher than normal and, in the single curve plotted, the sugar goes up to 240 mg. per hundred cubic centimeters at the end of the first hour. Thalhimer and Updegraff [5] believe that there is a quantitative relationship between the sugar content of the blood and the spinal fluid in epidemic encephalitis. They emphasize the fact that all their blood sugar values were high and that some were definitely above normal. In the twenty-eight cases reported by them, the blood sugar varied between 115 and 297 mg. per hundred cubic centimeters, while the spinal fluid sugar varied between 54 and 234 mg. per hundred cubic centimeters. They also remark that the sugar of the spinal fluid shows an increase only when the blood sugar is above a certain level. These observers believe that there is a threshold level for the entrance of sugar into the spinal fluid similar to that maintained by the kidneys for sugar in the urine. Kraus and Pardee [6] in twelve cases of epidemic encephalitis

---

* From the laboratory of internal medicine in the Boston Psychopathic Hospital.

1. Bryan, A. W.; Cathcart, E. P.; Fitz, R., and Buler, C.: An Improved Alimentary Glucose Tolerance Test, J. Metabolic Res. **1**:549 (April) 1922.

2. Rowe, A. W.: Metabolism of Galactose; Threshold of Tolerance in Normal Adults, Arch. Int. Med. **34**:388 (Sept.) 1924.

3. Gray, H.: Blood Sugar Standards, Arch. Int. Med. **31**:241 (Feb.) 1923.

4. Alexander, M. E.: Epidemic Encephalitis, Arch. Neurol. & Psychiat. **6**:44 (July) 1921.

5. Thalhimer, W., and Updegraff, H.: Epidemic Encephalitis, Arch. Neurol. & Psychiat. **8**:15 (July) 1922.

6. Kraus, W. M., and Pardee, I. H.: The Serology of the Spinal Fluid and Blood in Epidemic Encephalitis, Arch. Neurol. & Psychiat. **5**:710 (June) 1921.

near the acute stage report the fasting blood sugar varying from 75 to 170 mg. per hundred cubic centimeters. Wilcox and Lyttle,[7] in eleven cases of epidemic encephalitis, found the fasting blood sugar to be from 81 to 143 mg. per hundred cubic centimeters and the spinal fluid sugar to vary from 51 to 121 mg. per hundred cubic centimeters.

Our cases have been studied by the "blood sugar tolerance test" of Janney and Isaacson,[8] in which the dose of glucose is based on the patient's weight (1.75 gm. per kilogram) and samples of blood are withdrawn one, two and three hours after the ingestion of glucose. Sugar determinations were made by the method of Folin and Wu.[9] Our results are shown in the accompanying table; all the significant laboratory data are included here. The Wassermann reaction was negative in every case. None of the patients had glycosuria. The accompanying reports of the cases give only positive clinical findings. Of the seventeen cases here reported only four of the patients were seen in the acute febrile stage, though in no case was the clinical diagnosis in doubt. It must be remembered that we are here dealing only with the mental sequelae of epidemic encephalitis and the possibility of these findings not being characteristic of the disease as a whole must be borne in mind.

In considering the results of these experiments one is struck by the number of "flat" and "high" curves. Gray's figures at the end of the first hour after the ingestion of glucose show that 50 per cent. of the figures lie between 110 and 160 mg. per hundred cubic centimeters, whereas only four of the twenty-four curves in these cases lie within these limits. In Gray's series only 13 per cent. of the figures were over 140 mg. while in this group 40 per cent. fall above this figure. This contrast is so striking that despite the small numbers it is statistically valid in demonstrating a deviation from Gray's normal group. If this group of patients is divided according to age there are eight children and nine adults. It seems significant that the preponderance of values above 160 mg. should occur in the latter group whereas the children tend to show the flat curve—possibly a reversion to the infantile type of curve coincident with the mental reversion observed in these cases.

Case 11 showed an interesting change toward the "normal" as the disease progressed from the acute stage. Case 17 also showed some change, which was coincident with clinical changes. Case 9 showed distinct clinical improvement at the time of the second curve which is nearer the norm than the first.

---

7. Wilcox, H. B., and Lyttle, J. D.: The Diagnostic Value of Sugar Concentration in Spinal Fluid, Arch. Pediat. **40**:215, 1923.

8. Foster, H. E.: Hyperglycorachia in Encephalitis, J. A. M. A. **76**:1300 (May 7) 1921.

9. Folin, O.: A Laboratory Manual of Biological Chemistry, New York, D. Appleton & Co., 1922.

Data in Seventeen Cases

Case	Sex*	Age	Weight in Pounds (Kilograms)	Date of Curve	Blood Sugar Curve, Mg. per 100 C.c.				Spinal Fluid						Remarks
					Fasting	First Hour	Second Hour	Third Hour	Albumin	Globulin	Cells	Mg. per 100 C.c. Total Protein	Mg. per 100 C.c. Sugar	Colloidal Gold Reaction	
1	♀	9	54 (24.5)	2/14/25	74	100	111	—	--	0	5	18	50	Negative	
2	♂	9	67 (30.4)	4/29/25	71	94	96	104	—	—	—	—	—	—	
3	♂	10	114 (51.7)	2/20/25	87	160	127	132	—	0	0	15	65	Negative	
4	♂	10	58 (26.3)	4/29/25	95	118	101	99	—	—	—	—	—	—	
5	♂	11	100 (45.4)	2/ 6/25	91	83	99	83	—	—	—	—	—	—	
6	♂	12	64 (29)	4/29/25	86	143	111	63	—	—	—	—	—	—	
7	♀	13	103 (46.7)	2/21/25	133	168	150	150	++	0	66	—	88	Negative	
8	♂	13	96 (43.5)	9/ 6/24	105	95	81	103	—	—	—	—	—	—	
9	♀	18	94 (42.6)	9/ 6/24	105	250	222	146	—	0	1	44	80	Negative	
				2/25/25	76	92	133	112							
10	♂	24	127 (57.6)	1/30/25	89	87	92	89	—	0	3	82	69	Negative	Glucose given by nasal tube
				2/18/25	88	200	127	85							Temperature 101.5 (rectal)
11	♂	24	143 (64.9)	2/ 9/25	100	250	186	138	—	0	5	22	75	Negative	Basal metabolic rate, —1%
				2/15/25	98	102	111	97							Basal metabolic rate, —2%
				3/12/25	81	98	106	80							Basal metabolic rate, +16% after thyroid extract for ten days
				3/27/25	87	118	118	105							
12	♂	25	131 (59.4)	3/26/25	94	92	108	84	—	—	4	45	91	Negative	
13	♂	31	110 (49.9)	1/21/25	133	103	87	80	—	1	22	74	64	Negative	
14	♂	31	152 (68.9)	3/27/25	84	116	113	100	—	—	—	—	—	—	
15	♀	32	143 (64.9)	2/11/25	120	216	148	91	—	0	3	69	82	Negative	
16	♀	34	208 (94.3)	1/15/24	105	—	138	116	++	0	1	—	79	Negative	
17	♂	34	161 (73)	3/31/24	105	238	227	207	..	...	..	..	..	..	Basal metabolic rate, —23%
				5/26/24	89	339	192	97							
				2/22/25	115	189	129	—							

* In this column, ♂ indicates male; ♀, female.

It seems evident from the foregoing that a disturbance in the sugar metabolism is associated with the underlying pathology of this disease. The blood sugar tolerance curve apparently is a more sensitive indicator of this disturbance than the spinal fluid sugar with which it is probably intimately connected. It is noteworthy that the fasting blood sugar values in this group are not high and that the same is true of the spinal fluid "sugars" though the latter are with two exceptions in the higher half of the normal range.

SUMMARY

1. Twenty-four blood sugar curves according to the technic of Janney and Isaacson were performed in seventeen cases diagnosed epidemic encephalitis or its sequelae.

2. The blood sugar curve in epidemic encephalitis and the post-encephalitic state was found to deviate from the best established norm with such frequency that we may conclude that there is a fundamental disturbance of the sugar metabolism in this disease.

3. The derangement of the sugar metabolism persists in patients suffering from mental sequelae of this disease.

REPORT OF CASES

CASE 1.—A girl, aged 9 years, was admitted, Feb. 11, 1925, with the complaint of boisterousness and running away from home. Five years before the patient had a febrile attack during which she slept for three days and three nights. Following this she was sleepy for six weeks. Since that time there had been twitching of the hands and feet and a complete personality change in that she became disobedient, disorderly, antagonistic, restless and ran away from home. The pupils were unequal, and the tonsils were prominent. On account of extreme overactivity and aggressiveness, the patient was committed to the Foxboro State Hospital, February 28, unimproved.

CASE 2.—A boy, aged 9 years, was admitted, April 28, 1925, with the history that in October, 1924, he had had a febrile attack on account of which he had to stay in bed for several weeks. During this attack he saw "two mothers" (evidently diplopia). Following the attack the patient became very sleepy during the day and used to fall asleep with his feet in the oven. Gradually personality changes became noticeable; he became aggressive, irritable, poor in school, hyperactive during the night and sleepy during the day. He began to drool copiously and attack the other children. He is still in the hospital.

CASE 3.—A boy, aged 10 years, was admitted, Feb. 19, 1925, with the complaint of drowsiness. Five months before the patient was ill and the family physician told the parents that the patient had chorea. There was no fever but there was constant twitching of the muscles of the face. He was ill for six days but felt poorly for two weeks. February 14, he began to complain of headache and immediately went to bed, where he had remained in a stuporous condition. His nose twitched and he slept most of the time. He only took a little liquid nourishment; had no fever; vomited several times. He was delirious for one day and had been incontinent. He had gradually improved. Since the attack of "chorea" in September, 1924, he is quite a different boy, irritable and with completely changed tastes, mode of life, sympathies and affections. He had to be away from school most of the term because he became nervous and forgetful. Examination showed nothing except generalized tremors. There had been gradual ethical deterioration—stealing, lying and a complete personality change.

CASE 4.—A boy, aged 10 years, was admitted, April 21, 1925, with the history that he had epidemic encephalitis in December, 1924, and was at the City Hospital during January and February, 1925. Following his discharge from the hospital he began to have frequent attacks at night in which he closed his fists until the nails cut the skin of the palm of the hand. Physical examination showed a sleepy, immobile expression of the face, a drooping posture and fine tremors of the extended fingers. During his stay in the hospital there was noted reversal of the sleep rhythm, lethargy, periods of restless agitation with an agonized expression of the face, occasional muscular tension, and short intervals of hyperpnea lasting only two or three respirations. The intellectual functions seem to be well preserved and there is no evidence of deviation of conduct. The patient is still in the hospital.

CASE 5.—A boy, aged 11 years, was admitted, Feb. 11, 1925, with the complaint of stealing. In 1919 the patient had whooping cough followed by the extreme desire to sleep most of the day. There was a history of diplopia at this time. Examination showed a fixed expression of the face and drowsiness. He is still in the hospital.

CASE 6.—A boy, aged 12 years, was admitted, April 21, 1925, with the history that in December, 1924, the family had noticed that he became very sleepy, refused to get up in the morning and slept until noon. At night he was not sleepy at all. In January the patient had a severe cold and was admitted to the children's clinic of the Massachusetts General Hospital where a diagnosis of epidemic encephalitis was made. Following discharge from the Massachusetts General Hospital in March, 1925, he was sleepy most of the time. At night he was talkative, irritable, at times violent and once attacked his father with a knife. In April, 1925, the patient was at the Long Island Hospital but he had to be discharged because he was attacking nurses and patients.

On physical examination a slight drooping posture was noticed, retardation of all movements and a sleepy, immobile facial expression. In the ward the patient showed marked untidiness, constant blowing of the nose, complete reversal of the sleep cycle and constant spitting. The mental examination was negative with the exception of ethical deterioration. The patient is still in the hospital.

CASE 7.—A girl, aged 13 years, was admitted, Feb. 12, 1925, with the history that she was admitted to the Boston City Hospital, Nov. 19, 1924, and that her condition had there been diagnosed epidemic encephalitis. The spinal fluid at this time showed 70 cells and 0.061 per cent. sugar. She was discharged, Dec. 30, 1924, unimproved. During her convalescence it was noticed that she became confused, dull and restless, and was not able to focus her attention. On admission she was drowsy and dozing most of the time. Occasionally she cried for a few minutes, then began to doze again. Physical examination showed a frail looking semistuporous girl. Abdominal reflexes were absent. There was some difference in the plantar reflexes, extension on the right being followed by flexion. After two weeks in the hospital the patient was still extremely drowsy and lethargic.

CASE 8.—A boy, aged 13 years, was admitted, June 30, 1924, with a complaint of fainting and yawning spells. In March, 1923, he had a febrile attack of a few days' duration which was thought to be a cold. Following the attack he became sleepy in school, poor in his studies and extremely restless at night, keeping the whole house awake by continuous activity. He made and remade his bed twelve times during the night. In April, 1924, he developed spitting and yawning habits as well as fainting attacks.

On admission the patient was extremely restless, constantly getting out of bed, throwing his head backward in a yawning-like motion and expectorating all around him. At night he was sleepless and overactive. The intellectual functions were intact. There was extreme scattering of the attention and lack of continuity of effort. During his stay at the hospital there was gradual deterioration, with almost continuous yawning spells, and he spit all over the ward, which made him a difficult problem. In January, 1925, he was transferred to the Danvers State Hospital, unimproved.

CASE 9.—A woman, aged 18, was admitted to the hospital, Sept. 4, 1924, with the complaint that she would not talk, that she sat in her room and fainted frequently. In June, 1924, the patient had a febrile attack that was thought to be tonsillitis. In the attack the patient complained of difficulty of vision. Following the attack she became very quiet and seemed to like to be alone. She refused to eat and slept very little. On admission the patient was stuporous and incontinent.

On physical examination, the pupils were unequal and reacted sluggishly to light through a very narrow arc. The tendon reflexes could only be obtained on reinforcement. The left knee jerk was easier to elicit than the right. The thyroid was slightly enlarged. The mental condition was that of a stupor. At times she obeyed very simple commands, but she was uncooperative and resistive during physical examination.

On the fifth day after admission, the patient seemed brighter and complained of having lost her memory. She asked one of her sisters when her head would be cut. After about three weeks in the hospital she became a little brighter, took more interest in her surroundings, and would answer simple questions by a nod of the head. The course varied for about two months between slight improvement and regression to a stuporous condition until December, 1924; since then she has shown improvement and is still in the hospital.

CASE 10.—A man, aged 24, was admitted, Jan. 16, 1925, with a complaint of confusion and stupor. There was no history of any acute infection. In September, 1924, the patient complained of being tired; he stressed the necessity of rest, and became somewhat seclusive and inefficient in his work. The family noticed that he became gradually more and more drowsy, occasionally accusing himself of inability to work. Physical examination showed an undernourished sick boy with swollen, bleeding lips and a red face. The temperature was 101. He had to be tube fed. He was very confused. There was gradual deterioration. The patient is now in the hospital, the condition essentially the same.

CASE 11.—A man, aged 24, was admitted, Jan. 13, 1925, with the complaint of drowsiness and sleepiness. In 1919, the patient had epidemic encephalitis and was sick for eight or ten months. He became irritable, restless and had constant headaches; since 1922 he had been under the care of the Veterans' Bureau. Examination showed a fairly well developed young man with generalized tremors, especially of the tongue and fingers, active reflexes, unequal pupils, slight swaying in Romberg's position and a stooping posture. He was restless, had frequent shiver-like tremors, and vague hallucinations, with a good preservation of intellectual functions. He fell asleep frequently and had to be awakened for his meals.

CASE 12.—A man, aged 25, was admitted, March 3, 1925, with the history that, on January 13, he had suddenly felt weak and had passed urine very frequently. February 21, he became very weak and excited: at this time sudorrhea was noted. He had to go to bed and in the morning complained of dizziness and severe headache. On the following morning he had a convulsion, tonic in type. He stayed in bed for four days and on the fifth day became unconscious. That night he threw himself on the floor and made a few jerky movements with hands clenched; this attack lasted for about five minutes. March 3, he had two spells in which he became rigid and stiff. He did not bite his tongue and was not incontinent. There was no history of vomiting nor diplopia. Physical examination was negative. The temperature was 103 F.

On admission, the patient appeared dazed and toxic, and remained motionless with eyes staring straight ahead. He answered only in monosyllables and by a nod of his head admitted visual hallucinations. On the third day after admission, the temperature dropped to normal and he became more alert, although he still had extreme difficulty in carrying out simple commands and in understanding and comprehending simple questions. There was a purposeless shifting in the direction of the eyes and head. He is still in the hospital.

CASE 13.—A man, aged 31, was admitted, Jan. 6, 1925, with a complaint of failing vision, confusion and restlessness. Dec. 20, 1924, the patient complained that "his eyes were blurry" and said that he saw double. December 21, an optician told him that he had a "twisted optic nerve." Since that time the patient had been extremely fidgety and the family noticed that since January 1 he had slept excessively. At night he jumped and twitched in his sleep. He was delirious and while at home he imagined that he was at work. He was a poorly developed and poorly nourished adult with small, irregular and unequal pupils which did not react to light or accommodation. He had vertical nystagmus and slight right external strabismus in the primary position. The eye movements were jerkily performed, and there were jelly-like nystagmoid movements on lateral fixation. There was poor convergence, especially on the right. Both external recti were weak, more so on the right; the left rectus was weak except on conjoined movement. Upward and downward movements were poorly done, and there was bilateral partial ptosis, the left greater than the right. There were poorly coordinated eye movements. The mental examination showed underactivity, slight stupor, vague delusions and hallucinations, and initial retardation of speech. The patient was discharged, Jan. 27, 1925, unimproved and in a state of slight confusion.

CASE 14.—A man, aged 31, was admitted, March 23, 1925, with the history that six years before he was in bed for a week during which period he perspired freely and was weak and had diplopia. About three years before he noticed trembling of his legs and later trembling of his arms and backache, which had persisted to the present time. For the last few years the patient showed some personality change, abnormal sex appetite, affective swings and irritability.

Physical examination showed a masklike expression of the face and slowing of the gait, with loss of associated movements, resembling the parkinsonian syndrome. There was a fine, constant involuntary tremor of the head, hands and legs. The pupils reacted poorly to light, better to accommodation. The tendon reflexes were decreased. During the patient's residence in the hospital a normal underactivity was observed, wtih a great deal of sleeping in the ward during the day, slight depression, vague delusions and general impairment of the intellectual functions in the field of reasoning and judgment. The patient was discharged after ten days, his condition unchanged.

CASE 15.—A woman, aged 32, was admitted, Feb. 7, 1925, with the complaint that she had ideas about the necessity of impregnation by a young man. Five years before she had an attack of influenza. Following this her husband noticed that she became very sleepy and fatigued easily. The family noticed that "her face had dropped." Her judgment became impaired. She became somewhat euphoric and entered into all kinds of business ventures without success.

On admission there was definite masklike expression of the face, generalized tremors, stooping, rigid gait and unequal pupils. Mentally she was clear, but she was slightly euphoric and had vague hallucinatory experiences. March 13, the patient was discharged to the Westboro State Hospital, unimproved.

CASE 16.—A woman, aged 34, was admitted, Jan. 10, 1924, with a complaint of weakness, tremors and visual hallucinations. Five years before she had two attacks of influenza which lasted over ten weeks, during which she was drowsy and saw double. Since that time, her friends noticed that she did not do her housework as well, and that she developed tremors and peculiar facial expressions. She had definite epidemic encephalitis with stupor four years before. On admission she showed a masklike expression, obesity, loss of associated movements in walking, a forward stooping posture, slow hesitating speech, transient tremors, sluggish pupils, hyperactive reflexes, and clog-wheel resistance to flexion. The whole picture was very suggestive of Parkinson's syndrome. January 13, the patient was committed to the Boston State Hospital, unimproved.

CASE 17.—A man, aged 34, was admitted, March 17, 1924, with the complaint that he did not answer questions. For three months before admission the patient became very quiet, silent and uncommunicative. On admission he was in a stupor. There was no fever. There was loss of associated movements in

walking, a masklike expression of the face, and an extremely profuse sebaceous secretion over the face, producing the typical "ointment face." There was extreme retardation in initiating the simplest movements, although the patient apparently had no difficulty in understanding commands. The mental status was that of a stupor with complete mutism. Tears welled up into his eyes when he made an effort to answer questions, and he paid no attention to his surroundings. He remained in bed for three months. After six months he began to talk in a low whisper, and there has been gradual improvement in that the patient has begun to move around and help with simple routine work. Gradually the parkinsonian facies has disappeared, but the mental state is still one of confusion and he is still in the hospital.

INTESTINAL CHEMISTRY

III. SALIVARY DIGESTION IN THE HUMAN STOMACH AND INTESTINES *

OLAF BERGEIM, PH.D.
CHICAGO

In estimating the importance of salivary digestion in man studies must be made on the human subject. The salivas of the dog and cat have little or no action on starch whereas human saliva is powerfully amylolytic. Salivary digestion in man is influenced by psychic factors and by conditions of mastication and of gastric motility which cannot be exactly simulated in lower animals.

Numerous experiments have been carried out on the digestion of starch by human saliva but very few attempts have been made actually to follow the course of this digestion as it occurs in the human stomach. Most of these few experiments have been merely qualitative or otherwise inadequate. The best work appears to be that of Müller,[1] who obtained the gastric contents following a test meal by expression and determined the percentage of soluble carbohydrate.

The present series of experiments were carried out using the retention stomach tube, which does not appear to have been previously used for this purpose. The subjects were dental students of apparently normal digestive function. They reported at 1 p. m. The stomach tubes were passed and residuums examined for free hydrochloric acid. In one case this was not present and the complete residuum was removed to exclude the possible influence of pancreatic amylase. Subjects were cautioned not to swallow saliva until food was given. The test meals consisted of 100 gm. portions of boiled and mashed potatoes or 75 gm. of bread without crust. Ferric hydrate equivalent to 0.15 per cent. of iron was mixed with the potatoes and an amount equivalent to 0.088 per cent. of iron was incorporated in the bread flour. The iron was used as a control on sampling, and being practically insoluble should have no effect on the course of digestion.

Subjects were requested to masticate in a reasonably thorough manner. The time required was noted. Fifteen minutes after the last food was swallowed (about half an hour after the first of the food was taken) and at fifteen minute intervals thereafter gastric specimens were

* From the Laboratory of Physiological Chemistry, University of Illinois College of Medicine.

1. Müller, J.: Ueber den Umfang des Stärkeverdauung im Mund und Magen des Menschen, Verhandl. d. Cong. f. inn. Med. **19**:321, 1901.

removed for examination. The experiment was discontinued after forty-five minutes as by this time salivary digestion had been stopped by the gastric acid.

Seven cubic centimeters of gastric contents were removed each time. One cubic centimeter was titrated for free hydrochloric acid, using Töpfer's reagent as the indicator. One cubic centimeter was tested for active amylase by adding 5 c.c. of 1 per cent. soluble starch and testing for undecomposed starch after two hours and after eighteen hours. The other 5 c.c. was used to determine the degree of digestion of the starch. For this purpose the specimen withdrawn with a graduated syringe was introduced at once into a test tube containing 15 c.c. of 0.5 per cent. hydrochloric acid and the whole mixed, thus stopping starch digestion. The mixture was made faintly alkaline to phenolphthalein and heated to boiling for several minutes to get as much as possible of the starch into solution, then cooled and made just acid with acid sodium phosphate solution. The mixture was shaken to obtain a uniform suspension and while still being shaken 5 c.c. portions were pipetted out by means of a pipet with a tip of rather large bore into a series of three test tubes. One portion was filtered at once and the reducing carbohydrate was determined: 1 c.c. of the filtrate was treated with 3 c.c. of 0.2 per cent. picric acid and 0.5 c.c. of 5 per cent. sodium hydroxid and heated on the boiling water bath for ten minutes; this was then diluted with 20 c.c. of water and compared in a colorimeter with a maltose solution of about the same concentration treated in the same way. The results were expressed as maltose and calculated to starch equivalent, 1 gm. of maltose hydrate being equivalent to 0.9 gm. of starch.

Another 5 c.c. portion was treated with 1 c.c. of saliva, incubated at 40 degrees C. for twenty-four hours, and the reducing sugar determined as before. The value obtained expresses practically complete digestion as far as amylase is concerned and the percentage of digestion of starch was calculated by using the reduction values thus obtained as a basis. Starch was, however, also determined in a number of cases by acid hydrolysis and titration of glucose formed; 10 per cent. higher values were obtained for total starch in this way presumably because the small amounts of resistant dextrins left by the amylase are hydrolyzed by the acid. Results are therefore also expressed as percentages of the total starch converted to maltose.

Iron was determined in the third aliquot by adding an equal volume of concentrated hydrochloric acid, allowing it to stand over night, adding a little acid extracted blood charcoal, filtering, and taking a 5 c.c. aliquot of the filtrate. This was treated with 2 c.c. of 2 per cent. potassium thiocyanate and water to make 10 c.c. The red obtained was compared with that of a standard ferric salt solution treated in the

same way. The ratio of total starch to iron was determined for the original test foods and for each gastric specimen. If there is any appreciable separation of the solid from the liquid portions of the digestion mixture, the iron, being practically insoluble, will follow the undigested starch. The total original starch was calculated for each specimen from the iron content, and the percentage of digestion was calculated using this value as a basis, as well as the percentage determined on the basis of the direct determination of digestible starch. Had there been any great variations in the starch-iron ratios due to stratification of contents or absorption of maltose it would have been necessary to consider the digestion percentages obtained as representing the minimum rather than the actual degrees of digestion. Thus, in any case the degree of salivary digestion would not be overestimated. It will be noted, however, that the variations in the starch-iron ratio were not sufficiently great to affect the significance of the results. Therefore, under the conditions of this test, the iron index may with a fair degree of safety be dispensed with and the procedure correspondingly simplified. Thus, the determination may be made in the course of a gastric analysis using ordinary bread as a test meal, and the examination may be further restricted to the half-hour specimen as most significant.

It will be noted from the accompanying table that from 54 to 84 (average 76) per cent. of the starch of the potatoes was converted to maltose during the course of normal salivary digestion, and that from 46 to 68 (average 59) per cent. of the starch of bread was so converted. These figures leave out of consideration the fairly large proportion of soluble dextrins also formed so that the proportion of unaltered starch remaining is evidently small. Müller,[1] using rice mush as a test meal, found that from 59 to 80 per cent. of the carbohydrate was rendered soluble and with four normal subjects on a bread test meal found from 50 to 77 per cent. of the starch to be rendered soluble (less when the food was poorly masticated). It is evident, therefore, that if food is properly masticated a very considerable degree of starch digestion may be brought about by saliva.

Active amylase was observed after fifteen minutes in one of the six experiments on potatoes and three of the six experiments on bread, and in only one case in all was active amylase found at thirty minutes. That these findings are correct and that the method of sampling in general was quite adequate is shown by the uniformity of the results and especially by the failure to find any considerable maltose formation after the thirty minute period. Active amylase was found only when no free hydrochloric acid could be detected. It is evident that salivary digestion was generally at a standstill about fifteen minutes after the meal was finished and that the considerable degree of starch hydrolysis

obtained was due more largely to the high digestive activity of the saliva than to a prolonged period of action in the stomach.

The extent to which the salivary enzyme may contribute to the intestinal digestion of starch is not yet definitely known. Obviously, if much intact saliva with its high amylolytic power reached the intestine it would be capable of supplementing to no inconsiderable extent the pancreatic amylase. Such would be the case in subjects showing marked hyposecretion of gastric juice and even under conditions of normal gastric secretion it is possible that some unaltered saliva may reach the intestine through the relatively empty stomach or be washed through by water. It is further possible that small amounts of amylase may be adsorbed by raw starch and thus partially protected from the destructive action of the gastric acid.[2]

It would appear to be sufficiently established by the work of many investigators that amylase is destroyed by very low concentrations of hydrochloric acid, much lower in fact than those found in normal gastric contents at the height of digestion. Nevertheless, Pastore [3] has quite recently published observations indicating that salivary amylase may remain active in 0.12 per cent. hydrochloric acid and is not destroyed by 0.25 per cent. acid nor by 0.5 per cent. acid in the presence of starch. Furthermore, we still find quoted in textbooks the observations of Roger [4] that saliva inactivated by acid (or by boiling) may be reactivated by small amounts of added amylase and hence may be reactivated by pancreatic amylase in the intestine.

As a check on the conclusions of Pastore the following experiment was carried out:

Five cubic centimeters of saliva was added to 100 c.c. of 10 per cent. soluble starch. After fifteen minutes the solution, which showed erythrodextrin but no starch, was neutralized, 10 c.c. of 1 per cent. starch added and hydrochloric acid to make 0.05 per cent.; then the whole was incubated for fifteen minutes at 40 degrees C. The solution was neutralized to litmus, reincubated, and tested at intervals for undigested starch. Starch was still present after forty-eight hours, although it should have disappeared in ten seconds if the salivary amylase had not been destroyed.

It is evident from this experiment that large amounts of starch and its digestion products do not protect salivary amylase from destruction

2. Maestrini, D.: Atti d. r. Accad. d. Lincei, Roma **29**:391, 1920; Chem. Zentralbl. **3**:184, 1921.

3. Pastore, S.: Atti d. r. Accad. d. Lincei, Roma **29**:271, 1920; Chem. Zentralbl. **3**:184, 1921.

4. Roger, H.: Compt. rend. Soc. de biol. **62**:83; 1021, 1907; Rev. gén. d. sc. **18**:544, 1907.

Subjects 1 to 6 received 100 gm. of mashed potatoes; subjects 7 to 12 received 75 gm. of bread.

		Gastric Contents After 15 Minutes					Gastric Contents After 30 Minutes					Gastric Contents After 45 Minutes				
				Completeness of Starch Digestion, per Cent.					Completeness of Starch Digestion, per Cent.					Completeness of Starch Digestion, per Cent.		
Number	Time of Eating, Minutes	Free Hydrochloric Acid, per Cent.	Amylase	From Iron Ratio	Direct	Total Starch Converted to Maltose, per Cent.	Free Hydrochloric Acid, per Cent.	Amylase	From Iron Ratio	Direct	Total Starch Converted to Maltose, per Cent.	Free Hydrochloric Acid, per Cent.	Amylase	From Iron Ratio	Direct	Total Starch Converted to Maltose, per Cent.
1	10	0.07	—	30	30	27	0.24	—	49	49	44	0.27	—	62	60	54
2	12	0.09	—	79	82	74	0.11	—	82	86	77	0.01	—	91	92	83
3	10	0.12	—	89	91	82	0.15	—	98	98	88	0.30	—	93	93	84
4	14	0	+	76	74	67	0.06	—	89	87	78	0.14	—	88	84	75
5	12	0	—	100	100	90	0.25	—	91	90	81	0.33	—	92	90	81
6	18	0.15	—	84	79	71	0.26	—	90	87	78	0.28	—	92	90	81
Average	13	0.07	..	76	76	69	0.18	..	83	83	74	0.22	..	86	85	76
7	18	0	+	73	74	67	0	+	66	67	60	0	+	70	71	64
8	21	0.07	—	46	52	47	0.05	—	51	57	51	0.11	—	60	61	55
9	17	0.01	—	57	57	51	0.01	—	61	65	59	0.10	—	55	51	46
10	12	0	+	47	49	44	0.07	—	52	56	50	0.11	—	61	60	54
11	15	0.04	—	75	68	61	0.07	—	61	59	53	0.09	—	62	63	57
12	18	0	+	72	74	67	0.02	—	76	76	69	0.02	—	74	75	68
Average	17	0.02	..	61	62	57	0.04	..	61	63	57	0.07	..	64	64	59

by acid and that the digestive power is in no measure regained by neutralization. The experiments of Roger were repeated as follows:

Five cubic centimeter portions of saliva were treated with equal volumes of 0.5, 0.25, and 0.12 per cent. hydrochloric acid for two hours at 40 degrees C. The mixtures were neutralized to rosolic acid and diluted to 50 c.c. Ten cubic centimeter portions were placed in each of three flasks and in each of three other flasks 10 c.c. of water and 0.3 c.c. of a solution containing 0.3 per cent. sodium chlorid and 0.02 per cent. disodium phosphate to approximate the electrolyte concentration of the saliva. One cubic centimeter of 1:100 saliva was added to each flask together with 50 c.c. of 2 per cent. starch paste and all were incubated for one hour and forty minutes at 35 degrees. The maltose in each flask was accurately determined by iodin titration of reduced copper oxid.[5] The number of milligrams of copper reduced was for the first three flasks 77.5, 58.7, and 58.1, respectively, and for the three control flasks 72, 81.2 and 69.6, respectively. These results show practically identical amounts of maltose formed although a pronounced difference would have been observed if even 1 per cent. of the salivary amylase had been reactivated.

It is evident from this experiment that saliva inactivated by acid is not reactivated by amylase and that the findings of Roger were due to failure to consider the electrolyte concentrations of his digestion mixtures. We have shown the same thing to be true of Roger's experiments on boiled saliva. When electrolyte was supplied, as in the experiment just described, the digestion of starch to the achromic point required a shorter time (one and one-half hours) than when boiled saliva was added (one and three-fourths hours). There was no activation of boiled saliva.

Maxwell[6] and Nakagawa[7] have observed that the digestion of protein in vitro by artificial or natural gastric juice was delayed by starch but not by the products of starch hydrolysis, presumably because of adsorption of pepsin by the colloidal starch when this was present. The salivary digestion of starch may therefore promote the gastric digestion of protein.

In disease we may expect salivary digestion to be influenced by the quantity and digestive power of saliva secreted and by the motility and secretory power of the stomach. Obviously, in achylia salivary diges-

5. Sherman, Kendall, and Clark: J. Am. Chem. Soc. **32**:1087, 1910; ibid. **33**:1947, 1911; ibid. **34**:317, 1912.

6. Maxwell, L. A. I.: The Relation of Salivary to Gastric Digestion, Biochem. J. **9**:323, 1915.

7. Nakagawa, T.: The Relation of Salivary to Gastric Secretion, Biochem. J. **16**:390, 1922.

tion in the stomach will be undisturbed and will proceed to practical completion for this type of digestion. If the stomach possesses a bulky and highly acid residuum, such as sometimes found in ulcer with retention, or if the secretory response of the stomach is rapid salivary digestion will evidently stop sooner than it otherwise would. The observations of Müller, as well as our own, indicate that a rapid development of gastric acidity is not incompatible with a high degree of salivary digestion because if food is properly masticated and starch digestion allowed to proceed for fifteen minutes or so in the stomach almost as much starch is broken down as when digestion can proceed for a longer time. For this the high amylase concentration of saliva is responsible.

The amylolytic power of saliva in various diseases has been studied by Carles and Delmas-Marsalet,[8] who found low values in cachectic states, such as tuberculosis, and higher values in ulcer, indicating some parallelism with gastric chemistry. Probably more significant than quantitative changes in amylase concentration are variations in quantity of saliva secreted, and lowered salivary secretion may be expected in conditions diminishing body secretions generally, including gastric secretion. A diminished salivary secretion naturally calls for a longer period of mastication and the use of foods, such as acid fruits, stimulating salivary flow may be helpful.

Mention should be made of the work of Strauz,[9] who compared the digestion of food containing raw starch when masticated in the usual way and when introduced by stomach or duodenal tube, thus avoiding the influence of saliva. In cases of fermentative dyspepsia and of pronounced hypermotility of the stomach and intestines, he found less starch in the feces when the food was masticated. In other gastrointestinal disorders and in normal persons, no difference could be noted.

It must of course be borne in mind that the importance of the proper mastication of foods lies not merely in improving the ultimate utilization of starch. Comminution of food is of obvious importance. Mastication stimulates gastric secretion, which in turn stimulates pancreatic secretion. We may expect a more rapid utilization of foods, leaving less of these to pass into the lower bowel and become subject to bacterial action. Motor as well as secretory activities of the gastrointestinal tract are closely correlated, and disturbance of the initial digestive function may affect the whole digestive rhythm.

---

8. Carles, J., and Delmas-Marsalet, P.: Variations du pouvoir amylolytique a la salive au cours d'etaits pathologiques divers, Compt. rend. Soc. de biol. **91**:42 (June 13) 1924.

9. Strauz, L.: Ueber den Einfluss der Ausschaltung des Mundspeichels bei Magen- und Darmkranken, Arch. f. Verdauungskr. **33**:163, 1924.

SUMMARY

1. The extent of salivary digestion of the starch of a test meal may be determined in the course of a gastric analysis, using the retention stomach tube.

2. Bread or other foods containing a known amount of iron oxid may be used in studies of gastro-intestinal digestion and absorption, iron determinations serving as a guide in interpretation of the results.

3. Studies of salivary digestion in the stomachs of normal men showed on the average 76 per cent. of the starch of mashed potatoes and 59 per cent. of the starch of bread to be converted to maltose, an additional percentage being changed to dextrins.

4. This considerable degree of starch conversion was generally brought about within from fifteen to thirty minutes after the meal was finished, active amylase disappearing and free hydrochloric acid appearing simultaneously.

5. Salivary amylase is inactivated by low concentrations of free hydrochloric acid even in the presence of starch and its digestion products and does not again become active when the acidity is neutralized. Neither is it possible to reactivate, by the addition of small amounts of active amylase, saliva that has been inactivated by acid or by boiling. To function in the intestine saliva must escape the action of acid gastric juice.

PARALLELISM IN THE TREATMENT OF TUBERCULOSIS AND CARDIAC DISEASE

HORACE JOHN HOWK, M.D.
MOUNT MCGREGOR, N. Y.

The outstanding and gratifying phenomenon in the eradication of chronic disease—the decline in the tuberculosis death rate during the last two decades—invites serious attention to the malady that has supplanted tuberculosis as "captain of the men of death." Although tuberculosis still ranks among the major killing diseases and is exceeded only by heart disease and pneumonia, its past steady decrease is an almost certain augury of continued lessening of its menace and suggests that we be prepared, as tuberculosis becomes a less grave problem, to place in the campaign against the new "captain of death" as many as possible of the resources with which we have successfully fought the old.

The cut of more than half in tuberculosis mortality during the last twenty years brings into sharp contrast the situation with respect to mortality from heart disease, which has increased 31 per cent. in the United States during approximately the same period. This increase has been gradual and steady, with only one notable interruption, following the influenza epidemic of 1918, when the death rate in the United States dropped from 153.3 per hundred thousand in 1918 to 131 per hundred thousand in 1919. In 1900 the death rate from heart diseases in the registration area of the United States was 111.2 per hundred thousand. For the same area in 1922 the death rate was 148.4, and for the registration states in 1923 the rate had increased to 162.2. This rate includes all ages for both colored and white.

There are certain known and obvious causes of heart disease. The acute infectious diseases of children—acute rheumatic fever, chorea and scarlet fever—are notable for the frequency and manner in which they affect the heart. In the first three decades of life acute rheumatic fever is the most prominent causative factor. From the third decade on syphilis is an increasing cause of mortality; while in midlife the so-called degenerative diseases are the commonest cause of cardiac illness.

MORTALITY AT DIFFERENT AGE PERIODS

At all age periods of life cardiac disease is prevalent and crippling. After the fifth year in childhood the mortality rate steadily increases. At the age period from 10 to 14 the death rate from heart disease, in the experience of the Metropolitan Life Insurance Company among

twenty-four million industrial policyholders, exceeds the combined death rates for the four principal diseases of childhood, and is surpassed only by tuberculosis. At the ages from 35 to 44 one white person in every thousand living dies of heart diseases, while at the ages from 55 to 64 six of every thousand living die of cardiac disease. Among colored people the death rate is higher than among whites, in the company's experience the colored death rate averaging about twice as high as for whites at the age periods from 25 to 54.

TABLE 1.—*Death Rates Per Hundred Thousand for Organic Diseases of the Heart in the U. S. Registration Area from 1900 to 1923*

Year	Death Rate per Hundred Thousand	Year	Death Rate per Hundred Thousand
1923	162.2*	1911	141.1
1922	148.4	1910	141.5
1921	140.9	1909	129.7
1920	141.9	1908	128.3
1919	131.0	1907	137.5
1918	153.3	1906	127.6
1917	153.8	1905	131.3
1916	150.6	1904	133.4
1915	147.6	1903	124.5
1914	142.2	1902	117.3
1913	138.9	1901	113.4
1912	142.8	1900	111.2

* Registration states.

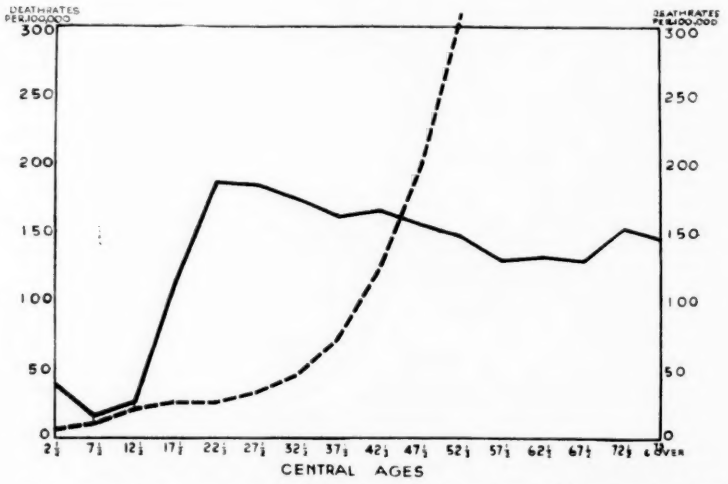
TABLE 2.—*Death Rates Per Hundred Thousand for Organic Diseases of the Heart in the Metropolitan Life Insurance Company Industrial Department for 1923 by Color, Sex and Age and in the Registration States for 1922 by Sex and Age*

Age Periods	Metropolitan Life Insurance Company Industrial Department				U. S. Registration States	
	White		Colored			
	Males	Females	Males	Females	Males	Females
All ages	112.2	120.9	189.6	216.1	151.2	146.5
Under 5	7.7	6.6	20.7	11.0	10.6	9.4
From 5 to 9	10.3	10.8	17.5	10.8	8.8	9.6
From 10 to 14	19.8	23.2	28.9	16.0	13.7	16.8
From 15 to 19	27.6	23.9	28.4	19.3	18.3	18.7
From 20 to 24	23.9	25.2	27.6	38.1	18.2	20.3
From 25 to 34	39.6	32.4	68.0	58.7	25.2	29.8
From 35 to 44	86.6	70.7	180.3	184.7	59.6	63.1
From 45 to 54	253.3	184.9	424.6	470.4	167.1	150.3
From 55 to 64	681.3	525.6	831.9	948.8	447.9	396.2
From 65 to 74	1,719.9	1,545.4	1,595.6	1,641.1	1,210.1	1,118.6
From 75 and over	4,060.8	3,524.7	2,600.1	3,016.5	3,105.9	2,969.1

Contrasting the age periods at which heart disease and tuberculosis cause the greatest mortality, it will be seen that tuberculosis still holds first rank from the ages 20 to 40, while heart disease becomes the leading cause of death soon after the age of 40. And so great is the increase thereafter that in totality heart disease exceeds every other. In the company's industrial experience for 1923 the rising curve of heart mortality crosses the declining curve of tuberculosis mortality at the age of 45.

Thus, cardiac disease has come to be a seriously fatal factor in our economic life, sweeping off great numbers of persons at the height of their productiveness, and the extent of the problem is not fully revealed in tables showing the mortality from heart disease since there are great numbers of deaths each year, especially in the midlife periods, from apoplexy, nephritis and other diseases in which the heart is vitally affected and may be the cause of death.

While much work has been done and experience gathered to reveal the morbidity incidence of heart disease, as yet we have no completely satisfying data. There is available, however, the record of school inspections which show that 2 per cent. of school children examined have heart impairments of various kinds. If we may conservatively consider that 1 per cent. of the 30,000,000 school children in the United



Comparative death rate per hundred thousand in patients with tuberculosis and with heart disease in the industrial experience of the Metropolitan Life Insurance Company in 1923: solid line, tuberculosis; broken line, heart disease.

States are affected by heart disease, we can begin to realize the enormity of the problem affecting 300,000 children of school age who will carry this serious debility throughout their precarious lives.

As a gage of morbidity among adults we have the draft examinations of the Great War, which gave 2.6 per cent. rejections for heart disease among men from 21 to 31 years of age. The experience of the Metropolitan Life Insurance Company gives a rejection for heart disease of 2 per cent. of those examined each year. From these widespread examinations representing a cross section of our young adults in the case of the draft, and a large group of adults applying for insurance

in the case of the company, we may safely conclude that approximately 1,500,000 adults in the United States are affected by heart disease of such seriousness as to unfit them for heavy military duty or as sound insurance risks.

Whether the causes of these impairments be started in early life by acute infectious diseases, whether they be produced later by syphilis, or whether they fall within the wide range of degenerative conditions of midlife, the fact is that there are now about one-fiftieth of our people who are ill, or will become ill, of heart disease, and whose mortality will lead all the rest of the brigade of death.

RECENT VIEWS OF SCIENTISTS AND CLINICIANS

The intensive study of heart disease within recent years by scientists and clinicians has modified and advanced our views concerning the nature of these ailments, and has emphasized the serious threat of heart disease at various periods of life. Through studies made in cardiac clinics, dispensaries and hospitals we have learned much that is now known of the life history of the cardiac patient. The statistical data that have been brought together and studied during this period have brought above the horizon many important facts respecting the mortality from heart disease in various periods of life and the seriousness of the situation as it exists at present. Unlike tuberculosis, the cardiac problem lacks the fear of infection and the consequent articulate demand by the profession and the public for segregation; this increases the difficulties of arousing general interest to its seriousness. Unfortunately, at present the cardiac patient rarely comes under observation in his home or in the dispensary or hospital, except when his symptoms are pronounced enough to interfere with his work or pleasure, and it is a common experience to find decompensation advanced to a point where symptoms are so severe as to interfere with his ability to undertake any productive activities. Naturally the future of such patients is precarious. The failure of their circulatory system is so pronounced that rehabilitation is greatly limited, if not impossible, and for a considerable part they drag out a dreary and shortened existence.

From a practical clinical standpoint we may divide patients with heart diseases, as we see them, into three classes: patients whose symptoms are of a mild nature and whose usual activities are interfered with only slightly, if at all; patients in whom symptoms have become more pronounced and are brought about more frequently and by less strain but who are yet able to maintain a moderate normal activity, and patients whose symptoms cause distress of various kinds which inhibits or wholly prohibits any physical activity. We have at present little appreciation of the earliest evidences of adult heart disease, notwithstand-

ing the great amount of study that is being given to this important problem. In many instances it is not difficult to trace symptoms back to early and milder stages of the disease which have progressed for months, or many years, with gradually increasing intensity, until the crippling breaks begin to appear. There are still woful gaps in our knowledge of the life history of cardiac patients owing, in part at least, to the present lack of facilities for concerted and prolonged study of these cases; indeed, there is no experience available that is comparable with the prolonged studies that have been made respecting the beginning and the course of tuberculosis.

It seems really doubtful whether any great progress can be made in the intelligent handling of this problem until we know more of the various factors that enter into the making and treating of the cardiac patient. At present there are few places outside of the home to which the cardiac patient can go for such prolonged treatment as he requires. The hospitals and dispensaries of the country are obviously inadequate in space for the care of these patients, whose observation and treatment should be prolonged for periods of weeks or months, and should contribute to the building up of a life history of the disease. So far as possible all etiologic factors, both physical and mental, should be searched for and corrected. Our present conception is that while there are general laws respecting the care and treatment of cardiac patients it is understood that there is no single standard, or group of standards, by which we can gage cardiac capacity. The treatment of heart disease, therefore, requires detailed individual study and testing of the patient before it can be known what powers for recuperation are available. Quite generally the cardiac patient has associated diseases that may be causative or resultant. On their recognition and treatment success or failure often depend. The syphilitic patient with his aortitis and secondary heart impairment is obviously unhelped unless his specific infection is minimized by treatment. When nephritis is associated with or underlies heart disease it, too, must have proper and continued treatment.

For the rehabilitation of the modern cardiac patient there is required a study of his past, observation of his present, and an estimation of his future capacities.

ADAPTABILITY OF TUBERCULOSIS SANATORIUMS FOR TREATMENT

The personnel and equipment of the modern tuberculosis sanatorium are peculiarly well adapted to the treatment of heart disease. Obviously there is lacking in heart disease the urge for segregation of the patient that has been so successfully employed in tuberculosis because of its infectiousness, and yet separation of the cardiac patient from the

environment in which he got sick is often quite as important from the standpoint of recovery as it has proved to be in the treatment of tuberculosis. To remove him from the usual worries and stresses in the home may be the first assured step in his convalescence. In our experience in the treatment of a large group of cardiac patients the elements of nostalgia and distress of separation from home have been no more prevalent or aggravating than in the tuberculous subject. The initiation and pursuit of a restorative regimen are comparatively easy and certain in an institution. The elements of cooperation and example, so helpful in the treatment of tuberculosis, are quite as potent and available in the care of cardiac patients. The average cardiac patient with mild or moderate symptoms should receive quite prompt and lasting benefit from the kind of treatment that can be supplied in tuberculosis sanatoriums.

Specifically the cardiac patient requires rest in bed. No remedy equals it. And the rest must be prolonged and observed. Only through persistent and sustained rest can recuperation begin. While resting the patient offers the required opportunity for study and the gathering of needed information of his physical disability, its nature and extent, and whether his circulatory system has ability to respond to treatment. This period of rest affords occasion for bringing together fragments of history that will form the pictorial background of the patient and will lead eventually to the accumulation of essential information of the life history of the cardiac patient.

Examination of the urine and blood is, of course, essential, and in many cases the determination of the chemistry of the blood and the renal function is required for the complete understanding of the diseased heart. Clinical instrumentation, including the use of the polygraph and the electrocardiograph, is helpful in differentiating various kinds and degrees of heart impairments.

When rest has served its purpose exercise is utilized to restore tone and efficiency to the circulatory apparatus and the body. Through exercise, graduated and controlled as to time, character and amount, one learns the physical capacities of the subject and to what extent he can adapt himself to a normal life. All the forms of occupation and exercise that have been employed in the tuberculosis sanatoriums are available and useful to restore the cardiac patient. Occupational therapy in its many forms has proved especially beneficial to the cardiac patient, both in bed and when ambulant. Walking, controlled by distance rather than by time, is a potent form of restorer to a weakened myocardium. Subsequently, and when restoration has been well established, more arduous forms of exercise may be employed, and especially in the milder cases.

In cardiac patients with associated nephritis diet becomes an important feature in the treatment. In many cases of midlife heart disease, overweight is a prominent associated factor—if not a causative one—and the reduction of the weight over a period of time requires careful dieting and guidance that the heart may not be further impaired. The provision of proper diet for the cardiac patient is quite within the possibility of any tuberculosis sanatorium; indeed, the facilities at present available in sanatoriums are ample to supply the required remedial agents in heart disease. No one knows better than the tuberculosis specialist the value and methods of administering rest; indeed, that has been the essence of success in recovery from tuberculosis, and the methods are thoroughly established. The careful prescribing of exercise to the tuberculous subject has been second only in importance to the value of prolonged rest, and the gradual restoration of strength through exercise has been amply experienced by all who have guided the convalescence of tuberculous persons.

Baths have been extensively used in spas in the treatment of some forms of cardiac diseases, and such baths as may be thought helpful can be readily and inexpensively reproduced in any institution.

Possibly the one outstanding objection to the treatment of heart disease in a tuberculosis sanatorium would be the fact that most sanatoriums are constructed largely to provide a maximum of out of door life, and obviously many cardiac patients cannot be treated out of doors in cold weather. Several modernly planned sanatoriums have aimed to provide a maximum number of enclosed rooms to permit isolation of tuberculous patients. In others, and this seems to be the modern trend, enclosed porches have been provided. In many institutions it would be possible to increase the number of heated rooms and wards, and this, without undue expense, would permit the care of any type of cardiac patient. Many patients with the early and milder forms of heart disease are not jeopardized by out of door life, especially in the warmer seasons; indeed, they are benefited by exposure to the open air. The types of heart disease requiring a uniformly mild atmosphere are those of badly broken compensation and those having an associated serious nephritis.

Moderate altitudes are not prejudicial to the treatment of cardiac subjects and it can be safely said that most such cases are not embarrassed at heights up to 1,500 feet.

CARE OF PATIENTS IN METROPOLITAN LIFE INSURANCE COMPANY SANATORIUM

Firmly believing in the suitability of the modern tuberculosis sanatorium for the treatment of heart disease, the Metropolitan Life Insurance Company in its Sanatorium at Mount McGregor, has for

several years cared for patients with these diseases as they have been recognized among the company's staff of employees. Ever since the dedication of the sanatorium in 1913 nontuberculous patients have been treated, but the majority of cardiac patients have been admitted during the last six years. Up to Dec. 31, 1924, 1,778 nontuberculous patients were admitted, of whom 440, or 24.7 per cent., had heart and arterial diseases. As employees of the company, the patients included only adults, and 26 per cent. of the cardiac patients were between the ages of 20 and 39, while 59 per cent. were in the age groups from 40 to 59; 13 per cent. were more than 60. Obviously this experience is not concerned with heart disease in children per se, but as the diseases of early years may be reflected into adult life.

The facilities for treatment are in the main similar to those found in most tuberculosis sanatoriums, consisting of an infirmary and open ward buildings. In addition there is one building with forty-seven beds in which prolonged treatment is given to patients with serious cardiac

TABLE 3.—*Primary Diagnoses and Complications in Arterial and Heart Diseases*

	Males		Females		Both Sexes	
	Number	Per Cent.	Number	Per Cent.	Number	Per Cent.
Total	330	100.0	82	100.0	412	100.0
Under 20 years	1	0.3	6	7.3	7	1.7
From 20 to 39 years	55	16.7	53	64.7	108	26.2
From 40 to 59 years	221	67.0	23	28.0	244	59.2
From 60 to 79 years	53	16.0	0	0	53	12.9

disease and to others. This building is similar in its plan to the general type of infirmary, save for the lessened porch space and the provision of rooms for one and two patients. Patients with the milder forms of cardiac disease and those without serious complications are treated in open wards.

From the standpoint of etiology the arterial sclerotic patient made up the largest class of patients treated. They comprised 46 per cent. of the total number and were found mainly beyond 40 years of age, often overweight, and many having high blood pressure and nephritis. These cases fall within the large general group of midlife degenerative diseases. The rheumatic patients formed 16 per cent. of the group treated, while the syphilis patients made only 3 per cent. of the group.

The general plan of treatment provides for complete bed rest of every admitted patient until the essential examinations have been made, the period of rest depending on the condition of the vascular system and the patient's response to treatment. In the sanatorium the period of bed rest has averaged forty-four days. The patient's physical resources are tested gradually to determine the limits within which he can exercise

without danger. This period of graduated exercise is continued persistently until it is demonstrated either that the vascular system has not enough resources to enable the patient to resume work, or until he can take up an occupation.

PRESENT CONDITION OF PATIENTS

Up to Dec. 31, 1924, 412 cardiac patients had been discharged from the sanatorium. The average period of treatment for this entire group was four months and twenty-six days. Briefly, the present condition of this group of patients is as follows:

Of the 412 patients, 198, or 48 per cent., are able to do full time work; thirteen, or 3.2 per cent., are carrying on modified work; 109, or 26.4 per cent., are unable to work, and seventy-nine, or 19.2 per cent., are dead. We were unable to trace thirteen, or 3.2 per cent., in time to incorporate their condition in this article. Many of these patients who are now working have undoubtedly been restored to full powers and efficiency through treatment in the sanatorium. They have had the

TABLE 4.—*Present Condition of 412 Patients with Heart Disease Discharged Up to Dec. 31, 1924*

		Per Cent.
Able to work	198	48.1
Able to do modified work	13	3.2
Unable to work	109	26.4
Dead	79	19.2
Unable to trace	13	3.1

required rest and exercise, have learned to adjust themselves to their impairment, and have acquired an experience in cardiac illness which enables them to keep well within their physical limitations in the stresses of a reasonably normal life. As in the treatment of tuberculosis so in heart disease, the great accomplishment is to teach the patient to accommodate himself to his disability. And yet these figures show more clearly than anything I can say the present serious state of the cardiac patient. In our studies and examinations of a circumscribed group of more than 30,000 employees working throughout the United States and Canada, we are making a serious effort to find the early cardiac patient. We have come to appreciate the difficulties in the way of bringing our cardiac patients under treatment when the best rehabilitation is possible and only now are we beginning to see the results of this effort. Somehow, notwithstanding its calamitous ways, heart disease has seemed to lack the threat that tuberculosis has held for the public for many years. But gradually this considerable group is beginning to appreciate the prevalence of heart disease and its crippling nature. They are learning

what every one must learn—that heart disease brings prompt and almost certain reduction in earning capacity and economic usefulness as well as enjoyment of life.

From this isolated and quite novel experience the treatment of heart disease in a tuberculosis sanatorium has been demonstrated as possible and satisfactory. To the patient has come an opportunity, similar to that provided the tuberculous patient, to acquire the maximum recovery of which his organism is capable; to learn his physical capacities and limitations, and, most important, to prepare for his adjustment to the environment in which he lives and works. In the study and treatment of the cardiac patient, there awaits the physician whose interests have been centered on chest diseases a new medical interest, stimulating, absorbing and rewarding.

THE VITAL CAPACITIES OF ONE THOUSAND SURGICAL PATIENTS *

HERMAN J. MOERSCH, M.D.

ROCHESTER, MINN.

The function of respiration has commanded the attention of physicians from the earliest history of medicine, and many fascinating theories were expounded in ancient times to explain it. Galen probably was the first investigator to have an approximately correct conception of its purpose. Nevertheless, for 1,500 years or more, the truths he advocated were disputed and submerged by superstition. It may be safely stated that the first great epoch in our knowledge of respiration began with the investigation of the circulation by Harvey and the publication of his first work in 1628. It was about two centuries later that studies were made on the vital capacity of the lungs and, while studies had been previously made, it was not until the appearance of the classical monograph by Hutchinson [1] in 1846, "On the Capacity of the Lungs and on the Respiratory Functions with a View of Establishing a Precise and Easy Method of Detecting Disease by the Spirometer," that its study was placed on a sound basis. The more one studies this classical article, the more one realizes that what we know today regarding vital capacity of the lungs was either established or foreshadowed by him. The minuteness of his observations, the multitude of tests and the great care he exercised in establishing normals to check his observations may well serve as a model for scientific work today. His closing remarks reveal his modesty and restraint.

> The matter of this communication is founded upon a vast number of facts—immutable truths, which are infinitely beyond my comprehension. The deductions, however, which I have ventured to draw therefrom, I wish to advance with modesty, because time, with its mutations, may so unfold science as to crush these deductions and demonstrate them as unsound. Nevertheless, the facts themselves can never alter nor deviate in their bearing upon respiration—one of the most important functions in the animal economy.

In recent years, especially since 1917, there has been a general revival of interest in the study of vital capacity. This renewed interest is primarily due to the work of Peabody and Wentworth [2] of this

---

* From the section on medicine, Mayo Clinic.

* Abridgment of thesis submitted to the faculty of the University of Minnesota Graduate School of Medicine in partial fulfilment of the requirements for the degree of master of science in medicine, March, 1925.

1. Hutchinson, John: On the Capacity of the Lungs, and on the Respiratory Functions, with a View of Establishing a Precise and Easy Method of Detecting Disease by the Spirometer, Tr. Med. Chir. **39**:137-252, 1846.

2. Peabody, F. W., and Wentworth, J. A.: Clinical Studies of the Respiration, IV, The Vital Capacity of the Lungs and Its Relation to Dyspnea, Arch. Int. Med. **20**:443-467 (Sept.) 1917.

country and Dreyer [3] of England. The literature on the subject since 1917 has become extensive, both from the clinical and the investigative aspects, and has been chiefly concerned with the determination of the normal capacity. The objection to the majority of observations is that they are made on healthy young college students and then applied to every age and walk in life.

In order to secure a wider and better conception of the value, applicability and accuracy of determinations of vital capacity, and the influence of diseases not involving external respiration, it was decided to make observations on a more heterogeneous group of persons. Accordingly observations were made on 1,000 consecutive adult patients who came for surgical treatment to the Mayo Clinic, irrespective of age, occupation, sex, stature, degree of physical fitness or walk of life.

TECHNIC

The spirometer used in making the determinations in this study was of the wet type and especially constructed at the Mayo Clinic (Fig. 1). By means of this instrument it is possible to determine within 8 c.c. the amount of air expired. It is so delicately balanced that the slightest inspiration is recorded on the scale. A spring cock valve at the opening into the tank permits control of the intake or outlet of air at any point in the respiratory cycle. The mouthpiece of the instrument is of nickel, may be easily and rapidly sterilized, and is so constructed that it can be held in the mouth firmly enough to prevent leakage. The subjects were instructed to inspire and expire as deeply as possible, to keep the nose closed, and to expire at a fairly uniform rate, thus preventing any possible escape of air around the mouthpiece. A nasal slip was not used because patients frequently complained that it annoyed them. When there was leakage around the mouthpiece it was easily recognized by the fogging of the nickel.

The following measurements and facts were determined for each patient: age, sex, place of residence, height, weight, body surface and vital capacity, as well as the disease. The height was measured without shoes and the weight was determined without clothing. From three to five, and even more, determinations of vital capacity were made in each instance, the highest always being accepted. All patients were subjected to a complete and thorough physical examination.

All readings of vital capacity were made in the middle of the morning, with extraneous influences reduced to a minimum when possible. Friends and relatives were excluded from the room, especially in the case of women, as their attention seemed to be easily distracted from the test.

3. Dreyer, Georges: The Normal Vital Capacity in Man and Its Relation to the Size of the Body, Lancet **2**:227-240 (Aug. 9) 1919.

EXTRINSIC FACTORS INFLUENCING VITAL CAPACITY

Many investigators wish to discard the spirometer because of the difficulty in interpreting the readings. Furthermore, they advance the argument that even when the readings are interpreted correctly, they do not determine the nature or even the existence of disease. On

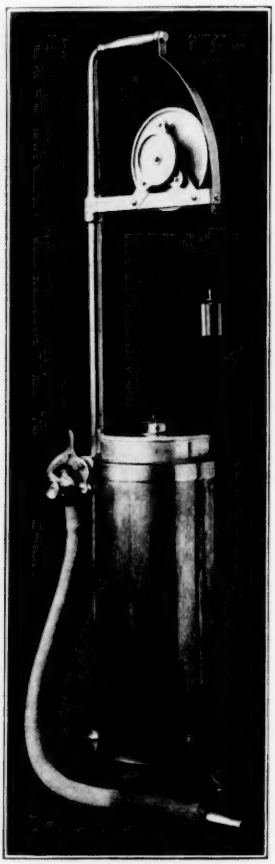


Fig. 1.—Spirometer used in work reported.

similar grounds there would be no justification for the recording of temperature, pulse rate or number of leukocytes. As a reduced vital capacity warns us that disease is present, especially in the heart and lungs, the use of the spirometer is as justifiable as that of the thermometer, blood pressure apparatus or blood counting chamber.

Posture.—Among the various extraneous influences that must be considered are: posture, season, temperature, atmospheric pressure, and race. The importance of position is shown if one accepts the dictum that vital capacities of 10 per cent. below the calculated normal indicate a pathologic state. Christie and Beams [4] found that the vital capacity taken in a reclining position averaged 5.5 per cent. below that taken in the sitting position. Peabody [5] asserts that the vital capacity should be taken with the subject either standing or sitting erect, as it is usually from 200 to 300 c.c. lower than when taken in the horizontal position. Rabinowitch,[6] in a series of fifty normal subjects, studied to learn the influence of posture, found a decrease in vital capacity varying from 20 to 600 c.c., and a mean decrease of 7.5 per cent. when they were in the recumbent position. Rubow [7] and also Hasselbalch [8] found that the vital capacity was greater in the standing than in the sitting position. On account of this variation, all the readings to be given were taken with the subject standing.

Time of Last Meal.—Hutchinson found that a full meal before the determination might decrease the vital capacity 200 c.c., or even as much as 38 c.c. Wittich, Myers and Jennings,[9] however, believe that a full meal does not exert an appreciable effect on vital capacity. I have seen reductions as great as 200 c.c. after a heavy meal, and believe the reduction is partially due to decreased effort associated with the discomfort of forced expiration when the abdomen is distended. After meals of moderate size, the variation is usually slight or absent.

Psychic Influences.—The psychic factor, as in many tests, is so variable an element, especially among female subjects, that it is difficult to estimate it. The least disturbance during the test caused in most instances a decided decrease in vital capacity. A certain group of middle-aged women apparently take pride in being considered below normal physically and do not put forth their best efforts. It is there-

4. Christie, C. D., and Beams, A. J.: The Estimation of Normal Vital Capacity, with Especial Reference to the Effect of Posture, Arch. Int. Med. **30**:34-39 (July) 1922.

5. Peabody, F. W.: The Clinical Importance of the Vital Capacity of the Lungs, Northwest Med. **22**:307-311 (Sept.); 350-352 (Oct.) 1923.

6. Rabinowitch, I. M.: The Vital Capacity in Hyperthyroidism with a Study of the Influence of Posture, Arch. Int. Med. **31**:910-915 (June) 1923.

7. Rubow, V.: Untersuchungen über die Atmung bei Herzkrankheiten, Ein Beitrag zum Studium der Pathologie des kleinen Kreislaufes, Deutsch. Arch. f. klin. Med. **92**:255-281, 1908.

8. Hasselbalch, K., quoted by Haldane, J. S.: Some Recent Advances in the Physiology of Respiration, Renal Secretion and Circulation, Brit. M. J. **1**:409-413 (March 19) 1921.

9. Wittich, F. W.; Myers, J. A., and Jennings, F. L.: A Study of the Effect of Pulmonary Tuberculosis on Vital Capacity, J. A. M. A. **75**:1249-1252 (Nov. 6) 1920.

fore necessary to try to eliminate these influences as far as possible. While certain persons are stimulated to greater effort by the psychic influence of competition, others show the opposite effect. Men especially seem to do better under the stress of competition. This was demonstrated by the following experiment. Six men were examined individually and the readings noted. Then they were all admitted to the same room at the same time and a contest instituted to see who could do the best. The previous readings were increased by several hundred cubic centimeters in all but one case.

INTRINSIC FACTORS

In spite of many and diversified formulas of normal variation advocated, it is improbable that any one will ever be evolved that can be regarded as normal for all persons, but if the various modifying factors, both intrinsic and extrinsic, are taken into consideration, a standard of normal variation will prove very useful. One objection to most standards is that they were based on studies of young healthy persons, in most cases with exceptional advantages for superior development. To advocate an arbitrary point below which everything could be regarded as pathologic indeed seems unjustifiable, as even among the normal persons a certain group falls below the usually advocated normal limit of from — 10 to 15 per cent. Myers and Myers,[10] in a study of 1,280 men at the University of Minnesota between the ages of 17 and 32, and 1,058 young women at the same institution, found 11.4 per cent. of the men and 27.1 per cent. of the women below 85 per cent. of their estimated normal vital capacity. While they ascribe the low readings to disease in the chest, inaccuracy of the normal standard and errors in recording, it would seem that the arbitrary normal is not applicable to all, but that each individual case must be considered separately.

The class of patients presented in this paper was therefore selected in preference because they represent something of a cross section of the human family. While it is true that they represent the diseased class, still I feel that it is a more representative group than a body of college students mostly in one period of life.

Sex.—Probably one of the most striking influences is that of sex. Hutchinson mentioned it as one of the four chief factors that influence vital capacity. Practically all formulas advocated for the estimation of vital capacity take this factor into consideration and make due allowance for the difference. On the average the capacity of men is about 20 per cent. higher than that of women. In children, as pointed out by

10. Myers, J. A., and Myers, F. J.: Studies on the Respiratory Organs in Health and Disease, IX, The Vital Capacity in a Group of College Men, Journal-Lancet **43**:276-277 (June 1) 1923.

Wilson and Edwards,[11] the difference is about 3.7 per cent. I have no figures to prove or disprove variations due to menstruation, and I have found none in the literature. Wittich, Myers and Jennings, however, found that pregnancy has no influence on the readings and although their group is small, their conclusions are well supported.

Age.—Hutchinson mentioned age as one of the chief factors influencing vital capacity but felt that it had less bearing than either height or weight. He stated that it increased up to the age of 30, and from 30 to 60 it decreased 43 cu. in., or 1.43 cu. in. a year. It is of interest to keep these figures in mind in relation to the variations found in the present group. Dreyer [3] asserts that age has little influence on vital capacity before the age of 50. Peabody and Wentworth,[2] Myers [12] and others have come to a similar conclusion. Bowen [13] believes that after fifty years there is a distinct gradual decrease, reaching 50 per cent. at the age of 85, the greatest drop occurring between 50 and 60. Pratt,[14] in a study of 100 normal men, concluded that the period of greatest

TABLE 1.—*Variation in Vital Capacity in One Hundred Normal Men According to Age (Pratt)*

Age, Years	Males	Average Vital Capacity, C.c.	Surface Area, Sq. M.	Percentage Variation from Normal Surface Area (West's Formula)
10-20	9	3,125	1.47	—18.0
20-30	14	4,500	1.72	+5.0
30-40	23	3,250	1.75	—10.0
40-50	20	3,775	1.81	—17.0
50-60	20	3,825	1.85	—17.0
60-70	11	3,300	1.80	—27.0
70-80	3	2,525	1.82	—44.0

capacity was in the third decade but that capacity did not fall much until the age of 60 (Table 1). The striking fact in Pratt's series is that in the aged the body surface was greater than in youth, while the height remained much the same, indicating greater weight for the same height; therefore obesity would be an associated factor in the decrease with age.

In classifying 1,775 males according to age, Hutchinson obtained the results in Table 2. The influence of age, as observed in this study, is in fairly close harmony with that observed by Hutchinson and is presented in Table 3 for comparison. For the sake of convenience and better evaluation, the cases are divided into two groups on the basis of sex.

11. Wilson, May G., and Edwards, D. J.: Diagnostic Value of Determining Vital Capacity of Lungs of Children, J. A. M. A. **78**:1107-1110 (April 15) 1922.

12. Myers, J. A.: Studies on the Respiratory Organs in Health and Disease, III, The Value of Vital Capacity Readings in Clinical Medicine, Minnesota Med. **4**:635-640 (Nov.) 1921.

13. Bowen, B. D., and Platt, D. L.: The Relation of Age and Obesity to Vital Capacity, Arch. Int. Med. **31**:579-589 (April) 1923.

14. Pratt, J. H.: Long-Continued Observations on the Vital Capacity in Health and Heart Disease, Am. J. M. Sc. **164**:819-832 (Dec.) 1922.

The variation between the ages of 20 and 60 is fairly uniform in all three groups. Between the years of 60 and 70, Pratt's figures would tend to show a rather sharp decrease in vital capacity as compared with my series. It may be said that there is a gradual decrease in vital capacity after the fourth decade and a more noticeable decrease after the fifth decade. With increasing age the number of persons with capacities above normal decreases, whereas the reverse is true with regard to persons with capacities below normal. Lemon and Moersch [15] and Arnett and Kornblum [16] have called attention to the fact that age must be con-

TABLE 2.—*Variation in Vital Capacity in One Thousand Seven Hundred and Seventy-Five Men According to Age (Hutchinson)*

Age, Years	Males	Average Vital Capacity, C.c.
15-20	283	3,608
20-30	838	3,624
30-40	413	3,633
40-50	148	3,272
50-60	67	3,084
60-65	26	3,001

TABLE 3.—*Variation in Vital Capacity According to Age in Four Hundred and Eighteen Males and Five Hundred and Eighty-Six Females with Number and Percentage Variation from Estimated Normal (West's Formula)*

			Males							
			Variation and Number Above and Below Estimated Normal Vital Capacity According to Height				Variation and Number Above and Below Estimated Normal Vital Capacity According to Surface Area			
Age, Years	Number	Average Vital Capacity, C.c.	Number	Plus	Number	Minus	Number	Plus	Number	Minus
15-20	4	5,019	3	21.6	1	8.0	3	16.0	1	9.0
20-30	58	4,759	44	16.4	14	10.4	46	13.0	2	10.4
30-40	111	4,608	83	14.1	28	12.6	75	12.2	36	13.1
40-50	122	4,422	71	11.5	51	9.8	61	10.5	61	11.0
50-60	86	4,215	44	12.9	42	15.5	40	10.1	46	17.0
60-70	35	4,071	12	11.0	23	12.6	8	8.5	27	14.5
70-80	2	3,968	1	3.0	1	11.0	1	0.0	1	15.0
			Females							
15-20	9	2,689	2	11.5	7	18.1	5	6.3	4	18.5
20-30	103	3,088	42	11.3	61	14.7	55	10.3	48	13.3
30-40	157	3,031	57	8.1	100	12.2	53	8.3	104	12.8
40-50	176	2,904	51	8.1	125	16.4	49	8.8	127	17.4
50-60	111	2,735	17	6.9	94	19.5	15	6.2	96	22.3
60-70	27	2,482	3	10.0	24	29.0	3	15.3	24	28.8
70-80	3	2,670	1	0.0	2	24.0	1	0.0	2	30.0

sidered in determining vital capacity, as the degenerative changes and the changes in height and weight which appear in advancing years provide many reasons for such a decrease, but they are such variable factors that they are difficult to evaluate. This is more readily understood when one considers that the ravages of age appear at varying times, earlier in some persons than in others.

15. Lemon, W. S., and Moersch, H. J.: Factors Influencing Vital Capacity, Arch. Int. Med. **33**:136-144 (Jan.) 1924.

16. Arnett, J. H., and Kornblum, K.: Vital Capacity: An Inquiry into Its Value as a Diagnostic Procedure, Ann. Clin. Med. **3**:255-274 (Oct.) 1924.

Height.—Hutchinson was the first to realize that the capacity of the lungs is dependent on certain bodily functions and to attempt to determine with which function it is most closely associated. He came to the conclusion that it is modified by four factors: height, weight, age and disease, height being the most important factor. He found that "for every inch of height from 5 to 6 feet, 8 additional cubic inches of air at 60 degrees are given out by forced expiration." The length of the trunk, the size of the chest as determined by plaster casts, the absolute capacity of the chest, and the depth of the thorax were found to have but little effect on the vital capacity. It has been stated by many observers that height bears a relationship to vital capacity, and there are many formulas for the estimation of the normal vital capacity from the height. Among

TABLE 4.—*Variation in Vital Capacity According to Height*

Height, Cm.	Number		Average Vital Capacity, C.c.	
	Males	Females	Males	Females
140-145	2	4	3,910	2,748
145-150	...	32	.....	2,521
150-155	1	85	3,798	2,709
155-160	11	181	3,708	2,786
160-165	57	166	3,801	3,030
165-170	92	84	4,170	3,245
170-175	121	19	4,589	3,180
175-180	97	8	4,712	3,533
180-185	35	...	5,121	.....
185-190	2	...	6,041	.....
190-195	1	...	5,735	.....

TABLE 5.—*Variation in Vital Capacity According to Height (Pratt)*

Height, Cm.	Average Vital Capacity, C.c.
150-155	2,900
155-160	3,150
160-165	3,400
165-170	3,725
170-175	3,950
175-180	4,300

the more common methods may be mentioned that of Peabody and Wentworth of dividing the males and females into three groups on the basis of height. Myers [17] introduced the use of an arbitrary numeral along with height for estimating the vital capacity, and West [18] used the same method. That such a relationship does exist may be seen from Table 4. It is interesting to compare the variations in height obtained in the present series with those obtained by Hutchinson eighty years ago (Table 5).

17. Myers, J. A.: Studies on the Respiratory Organs in Health and Disease, II, A Study of the Vital Capacity and Physical Fitness of Nurses, Journal-Lancet **41**:252-257 (May 1) 1921.

18. West, H. F.: Clinical Studies on the Respiration, VI, A Comparison of Various Standards for the Normal Vital Capacity of the Lungs, Arch. Int. Med. **25**:306-316 (March) 1920.

It can readily be seen in Tables 4 and 5 that there is a progressive increase in vital capacity with increase in height which, however, is not so marked in females as in males. The difference between the vital capacities at heights of 150 cm. and 180 cm. in Hutchinson's records was 1,150, and in the present series 1,004 c.c., which shows fairly close agreement for such a large group. The difference in vital capacities for the same height in Hutchinson's series and mine is more apparent than real, and can be accounted for by Hutchinson's reduction of all his readings to an atmospheric temperature of 60 degrees. This reduction to a uniform temperature was not made in my series.

Weight.—Weight, a factor that plays such an important part in the routine consideration of disease and often furnishes the clinician with an index of the general condition of the patient, is likewise found to influence vital capacity to a certain extent. Hutchinson observed that weight exerts an influence on vital capacity, but not as much as height. He found that "vital capacity does seem to increase from 100 to 200 pounds, and that between 105 and 155 pounds it increases 16.4 c.c. per pound in weight, and from 155 to 200 pounds this increase is overpowered and there is a loss of 39.5 cu. in. or 648 c.c." Hewlett and Jackson,[19] from a study of 400 college students, concluded that the correlations of vital capacity with height and weight are approximately equal, but it is not as accurate a correlation of vital capacity with the two together. Dreyer [3] felt that there was a closer correlation between weight and vital capacity than between height and vital capacity and presented mathematical proof of his contention. However, it must be said with regard to Dreyer's deductions that they were made on such a small group that their true value may be questioned. West, Myers, Peabody and Wentworth and Lemon and Moersch,[20] however, tend to agree with Hutchinson. The influence of weight on vital capacity as deduced from the present series is shown in Table 6, and it is discernible that there is not so close a relationship between weight and vital capacity as in Table 4 between height and vital capacity. Further, it may be noted that the increase is fairly uniform up to 150 pounds (68 kg.), but from there on tends to remain stationary or to decrease slightly, which is in agreement with Hutchinson's earlier deductions (Table 5).

Surface Area.—Surface area seems to bear a closer relationship to vital capacity than any other measurement of the body. However, the objection raised to the use of the formula based on surface area, devised by West, or the methods of Dreyer [3] or Hewlett and Jackson is that the

19. Hewlett, A. W., and Jackson, N. R.: The Vital Capacity in a Group of College Students, Arch. Int. Med. **29**:515-526 (April) 1922.

20. Lemon, W. S., and Moersch, H. J.: Comparison of Constants for the Determination of Vital Capacity, Arch. Int. Med. **33**:118-127 (Jan.) 1924.

calculation of the surface area is too complicated. This difficulty is easily overcome by the use of the chart constructed by Boothby and Sandiford for the determination of the surface area according to the DuBois formula (Fig. 2).

With this chart, all that is necessary is to connect the height and weight on the respective outside lines by means of a straight line and

TABLE 6.—*Variation in Vital Capacity According to Weight*

Weight, Kg.	Number		Average Vital Capacity, C.c.	
	Males	Females	Males	Females
30-40	...	8	.....	2,394
40-50	16	122	3,521	2,702
50-60	97	170	4,106	2,921
60-70	164	140	4,511	3,012
70-80	92	86	4,782	2,989
80-90	29	38	4,653	3,068
90-100	12	10	4,424	3,059
100 and up	7	7	4,412	2,792

TABLE 7.—*Variation in Vital Capacity According to Surface Area*

Surface Area, Sq. M.	Number		Average Vital Capacity, C.c.	
	Males	Females	Males	Females
1.20-1.30	...	4	.....	2,411
1.30-1.40	...	87	.....	2,532
1.40-1.50	17	108	3,647	2,750
1.50-1.60	28	119	3,647	2,895
1.60-1.70	90	127	4,202	3,010
1.70-1.80	109	81	4,475	3,018
1.80-1.90	80	60	4,815	3,142
1.90-2.00	62	17	4,776	3,158
2.00 and up	28	11	4,718	3,023

TABLE 8.—*Percentage Variation Between Vital Capacity Based on Surface Area and on Height (West's Formula)*

Method	Number Above Calculated Normal	Average Percentage	Number Below Calculated Normal	Average Percentage
Males				
Surface area	235	11.6	182	13.4
Height	257	13.7	160	12.4
Females				
Surface area	137	8.8	402	17.7
Height	176	8.9	407	16.7

read off the figures for surface area where it crosses the middle line. Table 7 shows the relationship of surface area to vital capacity, and it will be noted that vital capacity increases with surface area, and that as the effect or influence of obesity becomes apparent, the relationship digresses. That there is a rather close agreement between the relationships of surface area and height to vital capacity may be seen from Tables 7 and 8.

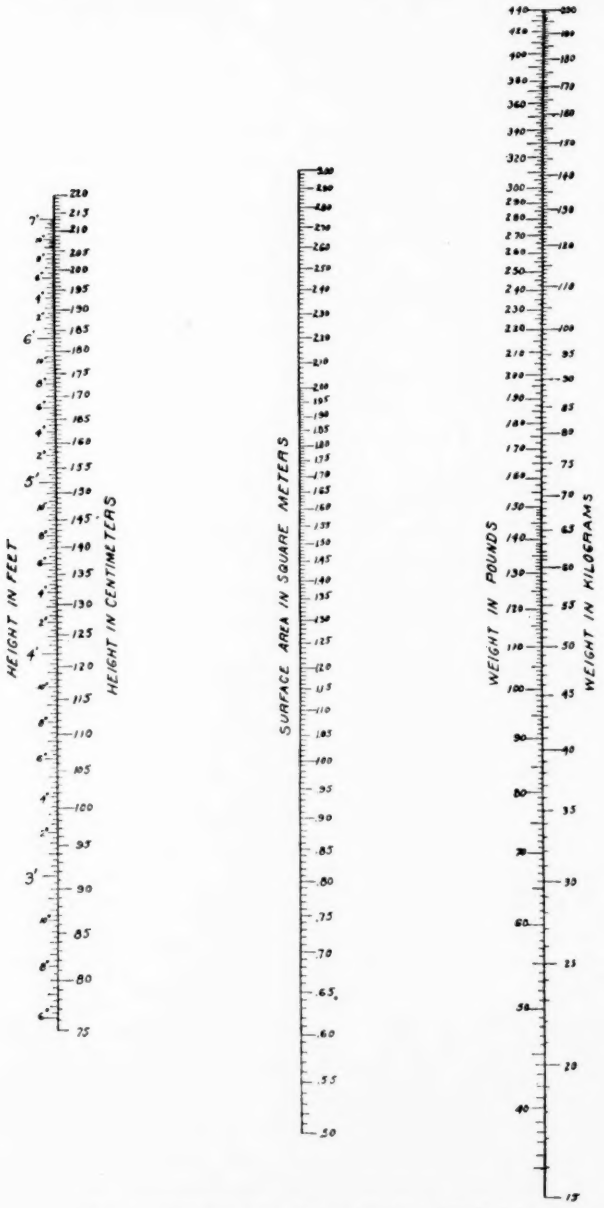


Fig. 2.—Surface area determinations (DuBois).

Variations in Vital Capacity Calculated from Height and from Surface Area.—In calculating the normal vital capacity in the 1,000 patients studied, it was decided to see how great was the difference between the vital capacity as calculated first by body surface and by height according to West's formula: surface area times 2.5 liters for men, and surface area times 2 liters for women, and height times 25 liters for men and 20 liters for women. If there was a close relationship, it would be more convenient to use the simpler method for routine purposes, especially as a chart for the calculation of surface area is not always available. The averages obtained from these two methods are presented in Table 9.

Organic Disease.—It is well known that certain diseases may cause a decrease in vital capacity. Anything that interferes with the respiratory movements of the thorax, pleural and pulmonary changes, cardiac dis-

TABLE 9.—*Percentage Variation in Vital Capacity Above and Below the Calculated Normal in Various Diseases*

	Males				Females			
Disease	Number	Per Cent. Above Normal	Number	Per Cent. Below Normal	Number	Per Cent. Above Normal	Number	Per Cent. Below Normal
Adenoma of thyroid	7	12.4	5	11.2	19	6.5	53	19.5
Appendicitis	28	14.0	12	9.2	20	10.0	38	15.5
Carcinoma of stomach	11	9.3	9	10.2	1	2.0	6	20.0
Carcinoma of bowel	17	11.4	9	15.0	2	5.0	4	19.8
Carcinoma of head and neck	2	21.0	6	8.7	..	....	..	....
Carcinoma of breast and all other tumors of breast	1	10.0	1	14.0	13	10.0	28	16.9
Carcinoma of uterus	..	....	..	....	3	10.0	8	14.6
Carcinoma, miscellaneous	2	22.0	0	0.0	0	0.0	3	19.0
Cholecystitis	19	13.3	15	13.3	28	8.5	63	11.4
Duodenal ulcer	60	14.2	32	10.4	9	7.9	11	14.0
Gastric ulcer	14	11.1	7	9.6	14	11.1	7	9.6
Hernia	22	16.0	16	8.6	1	6.0	11	20.9
Abdominal tumor	3	5.6	1	3.7	..	....	..	....
Pelvic and abdominal tumors	..	....	..	....	24	10.3	40	14.4
Kidney and bladder	20	13.5	30	12.7	2	3.0	11	16.3
Perineal and pelvic laceration	..	....	..	....	23	9.3	56	14.1

ease, hyperthyroidism, blood disturbances both chemical and cytologic, as well as prolonged infections, will cause a decrease in vital capacity.

Flexibility of Thorax.—Peabody and Wentworth first called attention to the influence of flexibility of the thorax on vital capacity. The ability of the lungs to fill with air is dependent on the flexibility of the thoracic walls. Ossification of the costovertebral joints, cartilage, and so forth, may therefore affect vital capacity by decreasing the flexibility of the thoracic cage.

Intra-Abdominal Pressure.—The effect of variations of intra-abdominal pressure on vital capacity is uncertain. It would seem probable that any condition in the abdomen that interfered with free movement of the diaphragm would influence it. Wittich, Myers and Jennings, and more recently Bell,[21] found that pregnancy has little influence on vital capacity.

21. Bell, J. W.: Personal communication to the author.

Equally important is the observation that Lewis [22] made in animals in deep anesthesia, that variation in abdominal pressure plays no part in the production of respiratory curves. Patients with large abdominal tumors uncomplicated by other diseases do not show an abnormal decrease in vital capacity. Therefore, it would seem that increased intra-abdominal pressure per se without involvement of the diaphragm has very little influence on vital capacity.

Pleural and Pulmonary Changes.—It is readily understood and easily demonstrated that anything that causes a decrease in the volume of the lung by retraction or displacement of the lung tissue will also cause a decrease in vital capacity, depending on the amount of tissue affected and the degree of interference with respiratory excursion or interference with the passage of air into other portions of the lungs. Hutchinson demonstrated this in 1846, in tuberculosis of the lungs. Since then Myers,[23] Hyge,[24] Shepard,[25] Dreyer and Burrell [26] have confirmed his observation and found that it varies fairly closely with the clinical and roentgenologic findings. Siebeck [27] believes that this decrease in vital capacity in tuberculosis is due to an increase in the volume of residual air, a decrease in the elasticity of the lung tissue and less forceful expiration. Myers,[28] Shepard, and Arnett and Kornblum found a rather marked characteristic drop in vital capacity in pneumonia, which is of especial diagnostic value in this condition. Myers,[28] Peabody and Wentworth found a decrease during attacks of bronchial asthma with a return to normal in persons in whom the condition was not associated with complications. Lemon and Moersch [15] also observed a decrease with pleural effusions, pneumothorax, tumors of the chest and lung, pleural adhesions, cardiospasm, diverticula of the esophagus, bronchi-

22. Lewis, Thomas: Studies of the Relationship Between Respiration and Blood Pressure, J. Physiol. **37**:233-255, 1908.

23. Myers, J. A.: Studies on the Respiratory Organs in Health and Disease, A Comparison of Lung Capacity Readings and Physical Signs in Pulmonary Tuberculosis, Minnesota Med. **5**:233-237 (April) 1922.

24. Hyge, T. V.: The Vital Capacity in the Tuberculous, Hospitalstidende **67**:341-350 (May 28) 1924.

25. Shepard, W. P.: The Effect of Certain Past Diseases on Vital Capacity, Arch. Int. Med. **33**:185-192 (Feb.) 1924.

26. Dreyer, Georges; and Burrell, L. S. T.: The Vital Capacity Constants Applied to the Study of Pulmonary Tuberculosis, Lancet **1**:1212-1216 (June 5) 1920.

27. Siebeck, Richard: Ueber die Beeinflussung der Atemmechanik durch krankhafte Zustände des Respirations- und Kreislaufapparates, Deutsch. Arch. f. klin. Med. **100**:204-220, 1910.

28. Myers, J. A.: Studies on the Respiratory Organs in Health and Disease, VI, The Significance of the Vital Capacity Test in Pulmonary Tuberculosis, Bronchial Asthma, Pneumonia and an Acute Infection Outside the Respiratory Tract, Arch. Int. Med. **30**:648-667 (Nov.) 1922.

ectasis, emphysema, abscess of the lungs, and various conditions involving the respiratory apparatus.

Hyperthyroidism.—Recently McKinlay [29] and Rabinowitch [6] have reported that a direct relationship exists between vital capacity and the severity of exophthalmic goiter and adenoma of the thyroid with hyperthyroidism, as expressed by the basal metabolic rate. On the other hand, Lemon and Moersch,[30] in a study of eighty-five patients with goiter, reported that no such relationship exists, the diagnosis in every instance having been confirmed by microscopic examination. Their conclusion was that one cannot accurately predict the decrease in vital capacity that will be associated with change in the basal metabolic rate.

So far as the decrease in vital capacity in hyperthyroidism is dependent on the degree of cardiac damage, it is evident from a study of a large series of goiter patients that no constant relationship exists between the basal metabolic rate and cardiac efficiency.

Diseases Not Related to the Respiratory Function.—It is also of interest to know what influence the general diseases that require operative treatment have on vital capacity, for if the disease itself does not influence vital capacity we have much more reason to employ it as a routine in the examination of patients undergoing operation, to detect a large group of pulmonary and cardiac diseases which might pass unnoticed and thereby increase the operative mortality. In Table 9 is a list of the diseases manifested by the patients examined in the present study and the percentage variations in vital capacity from the normal. The group showing hyperthyroidism and cardiac and gross pulmonary disease are excluded in the classification for reasons already mentioned (Table 9).

It may be readily seen that the diseases named influence vital capacity very little. It should be stated that in many cases a multiplicity of diseases existed in the same patient although the chief complaint is listed in each instance, so that even multiple disease not involving the organs of external respiration does not cause a decrease in vital capacity. Patients having twenty-eight different types of disease also were examined, but in none did there appear to be a definite relationship between the disease and vital capacity. It may therefore be seen that determinations of vital capacity are of particular importance in routine examination of operative cases in which the patient has not had the benefit of a thorough medical examination, as it gives a fairly accurate index of the efficiency of the organs of external respiration.

---

29. McKinlay, C. A.: The Vital Capacity of the Lungs and Its Significance in Hyperthyroidism, Arch. Int. Med. **34**:168-176 (Aug.) 1924.

30. Lemon, W. S., and Moersch, H. J.: Basal Metabolism and Vital Capacity, Arch Int. Med. **33**:130-135 (Jan.) 1924.

COMMENT

While many and diversified conditions, often of a baffling nature, require interpretation to obtain an accurate conception of the vital capacity of a subject, still the use of the spirometer fulfills a definite requirement in clinical medicine. While it may be truthfully said that determinations of vital capacity will not permit of a diagnosis without further data, when used as an adjunct to other clinical findings they may be of considerable importance. They are especially useful in following the course of cardiac and pulmonary disease. The greatest value of the spirometer lies in its ability to detect any disturbance of external respiration. Diseases that do not affect the cardiorespiratory functions have very little or no influence on vital capacity. This fact alone makes the spirometer of great value in the routine examination of patients or any large group of persons undergoing examination for physical fitness. While it will never be substituted for a thorough clinical and physical examination, still when this is not feasible or possible, it is a great aid in attracting the attention of the examiner to the possible presence of one of a large group of gross pulmonary or cardiac diseases. While in many instances a low vital capacity may exist without any demonstrable organic cause, in a large percentage organic disturbance involving the cardiorespiratory system may be demonstrated.

Clinicians and surgeons often tend to get out of touch with the patient's progress and often greatly overestimate his vitality. In long drawn out disease affecting the heart and lungs, frequent determinations of vital capacity will help to foretell the course of the disease. This is especially true when edema is present. When the patient is put to bed, the sudden disappearance of the edema may prompt a feeling that there has been a marked improvement. By the use of the spirometer it may be demonstrated in many instances that the disappearance of the edema is due to a shifting of fluid rather than to its actual absorption and excretion.

In the foregoing observations it has been my aim to point out the various factors that influence vital capacity and to show that diseases not involving respiration have no influence on vital capacity. Finally, through an accurate understanding of these influences, it has been my aim to demonstrate that if these influences are accurately understood, studies of vital capacity are of distinct clinical value.

CONCLUSIONS

1. Determinations of the vital capacity of the lungs should not be regarded as a diagnostic measure in itself, but rather as an aid to diagnosis, just as the use of the thermometer and sphygmomanometer are aids.

2. Various extraneous factors that influence vital capacity are: posture, size, time elapsed since last meal, and psychic disturbances.

3. Determinations of vital capacity are most accurate when calculated on the basis of surface area and height.

4. The relationships of surface area and height to vital capacity are so similar that for most practical purposes the standard based on height alone will prove satisfactory.

5. The vital capacity calculated on surface area tends to give higher values than that calculated on height alone.

6. No formula in itself has proved satisfactory in all cases, as normals may give readings below 85 per cent. of their calculated vital capacity. Therefore, it is not correct to regard every reading of more than 15 per cent. below normal as pathologic.

7. The same relationships tend to hold true in children as in adults.

8. Physical fitness, sex, age, height, weight and surface area influence vital capacity.

9. The number of pregnancies in a woman does not seem to influence vital capacity, the same being true of miscarriages.

10. Anything that interferes with or influences the normal functions and activity of the lungs has a direct bearing on the vital capacity.

11. Diseases not affecting or influencing the respiratory or cardiac system do not appreciably influence vital capacity.

THE REFRACTOMETRIC AND VISCOSIMETRIC INDEXES OF CEREBROSPINAL FLUID*

A. LEVINSON, M.D.
AND
A. M. SERBY, M.D.
CHICAGO

The determination of the refractive index of blood has been in use for several years owing to the work of Reiss,[1] Naegeli,[2] Rohrer[3] and many others. It seemed to us worth while to determine the refractive index of cerebrospinal fluid. The literature reviewed by us revealed so far only two references to such determinations, the work of Polanyi[4] and that of Molnar.[5] It was our hope that the refractive index of cerebrospinal fluid in various conditions might yield some data that would be found useful for diagnosis, as has been the case in blood.[1] In order to do the work along the same lines as has been done on blood, it was deemed advisable to do viscosimetric readings together with refractometric determinations. It also was hoped that the combination of the two, the refractometric and the viscosimetric indexes, might throw light on the albumin-globulin ratio of cerebrospinal fluid.

GENERAL CONSIDERATION OF REFRACTOMETRY AND VISCOSIMETRY

Refractometry as a means of determining the amount of dissolved substances in fluids has been in use for about fifty years. Originally it was applied to the quantitative determination of sugar solutions. Later it was applied to the quantitative determination of protein in the blood. The proteins in the blood constitute 87 per cent. of the dissolved serum substance. It was therefore believed and subsequently proved that except in extremely pathologic conditions, the blood salts, nitrogenous products and corpuscles can be disregarded in estimating the amount of dissolved proteins. The refractometric index in blood of normal persons has been found to vary between 1.34557 in infants under 1 month

* From the Otto Baer Fund for Clinical Research of the Michael Reese Hospital and the Nelson Morris Memorial Institute for Medical Research.

1. Reiss, E.: Die Refraktometrische Blutuntersuchung in ihre Ergebnisse für die Physiologie und Pathologie des Menschen, Ergebn. d. inn. Med. u. Kinderh. **10**:531-634, 1913.

2. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, Ed. 3, 1924, p. 39.

3. Rohrer, Fritz: Bestimmung des Mischungsverhaltnisses von Albumen und Globulin in Blutserum, Deutsch. Arch. f. klin. Med. **121**:140-221, 1916.

4. Polanyi: Beitrage zur Chemie der Hydrocephalusflussigkeit, Biochem. Ztschr. **34**:205, 1911.

5. Molnar, A. L.: Ueber die Refraktion der Menschlichen Lumbalflüssigkeit, Klin. Wchnschr. **2**:790-791 (April 23) 1923.

of age, corresponding to 5.6 per cent. of protein, and 1.35110 in older children and adults, corresponding to 8.8 per cent. of protein.[1]

In normal cerebrospinal fluid the amounts of protein, salts, nitrogenous substances and corpuscles are about equal in regard to their influence on the refractive index. As it is generally assumed that the proteins are the substances that are greatly increased in meningeal inflammations, we thought that the refractometer might serve to estimate this amount accurately.

The refractometer is an instrument that measures the deviation of light passing through fluids. Fluids refract transmitted light definitely and quantitatively according to the amount of dissolved substances. With the instrument we used, the Pulfrich dipping refractometer, determinations may be made with only 3 minims of fluid, a point of great importance in the study of cerebrospinal fluid. Readings are made from the scale of the instrument by means of a table and the readings are easily changed into the refractive index. Readings must be corrected to 17.5 degrees C. For full description of the mechanism and use of the instrument, the reader is referred to the work of Reiss.[1]

TABLE 1.—*Effect of Time Element on Refractometry and Viscosimetry*

Case	Disease	Time of Examination	Refractometric Index	Viscosimetric Index
1	Meningococcus meningitis.....	Immediately.....	1.33574	1.11
		After 24 hours.....	1.33574	1.11
2	Meningococcus meningitis.....	Immediately.....	1.33533	1.11
		Centrifugated 10 minutes, then examined immediately.....	1.33531	1.10
		After 90 hours.....	1.33533	1.11

The viscosimeter determines the viscosity of fluids. The fluid is sucked through one capillary tube while water is sucked through another tube of equal caliber. The reading is made with the tube through which water is sucked. The factors causing changes in viscosity, as in refractometry, are the dissolved substances. Correction must be made for the temperature to about 20 degrees C. The viscosity of the blood varies in normal persons from 1.43, corresponding to 5 per cent. protein, to 1.9, corresponding to 9.5 per cent. protein.

Allowing the fluid to stand several hours before examination apparently has no effect on the refractometric and viscosimetric indexes. Fluids from two patients with meningococcus meningitis which were allowed to stand for twenty-four and ninety hours, respectively, showed no change in either index at the end of that period (Table 1).

Centrifugating of the fluid immediately also produced no change in the indexes.

Bloody fluid, however, gives higher refractometric and viscosimetric indexes.

REFRACTOMETRIC INDEX

We examined 115 fluids obtained from ninety-three patients. These fluids were divided as follows: Sixty-six fluids were obtained from so-called normal patients, namely, patients who had no meningeal inflammation. We believe that one seldom obtains a real normal cerebrospinal fluid. The very fact that a fluid has to be withdrawn from the body indicates that there is some symptom leading to a suspicion of disturbances of the nervous system. We shall, therefore, designate this group of so-called normal cases as nonmeningitic. Sixteen specimens were taken from fourteen patients suspected to be syphilitic. Of these, three were found to be actively syphilitic and the rest had a negative Wassermann reaction, although they had a history of syphilitic symptoms or of previous syphilitic infection. Seven fluids were obtained from patients with tuberculous meningitis; fifteen fluids from three patients with meningococcus meningitis, and eleven fluids from seven patients with purulent meningitis other than meningococcal.

Nonmeningitic Fluid.—In a series of miscellaneous cases, such as rickets and appendicitis, in which there was either no involvement of the nervous system, or in which there were nervous manifestations that later proved to be nonmeningitic and nonsyphilitic, excepting compression myelitis and one case of hydrocephalus, the refractometric readings ranged between 1.33472 and 1.33545, with an average of 1.33508 (Table 2). These may be further subdivided into the following:

In four cases of Little's disease, the reading ranged between 1.33472 and 1.33529; in ten cases of epilepsy, between 1.33493 and 1.33517; in two cases of mongolian idiocy and one case of imbecility, between 1.33500 and 1.33514; in two cases of encephalitis, the reading was 1.33509 and 1.33511; in three patients recovered from encephalitis, the reading ranged between 1.33498 and 1.33527; in nine cases of pneumonia and otitis media, between 1.33478 and 1.33521; in seven cases of hypertension, between 1.33500 and 1.33532, in three cases of brain and spinal cord tumor, between 1.33509 and 1.33523, and in one case of congenital heart disease, the reading was 1.33545.

Hydrocephalus and Compression Myelitis.—In one case of ventricular fluid from a noncommunicating hydrocephalus, the reading was 1.33747; in two other cases, 1.33518 and 1.33511. In one case of compression myelitis, the reading was 1.33700. A comparison between ventricular and lumbar cerebrospinal fluid in one case showed a very slight difference in the reading.

Syphilitic Fluid.—In three cases of active syphilis and eleven cases of latent or inactive syphilis, the refractometric readings varied, the lowest being 1.33513. The upper range was 1.33557, the average being 1.33525 (Table 3).

TABLE 2.—*Refractometric and Viscosimetric Readings in Nonmeningitic Fluid*

Case	Disease	Age	Globulin	Cells	Wassermann Reaction	Colloidal Gold Test	Refractometric Index	Viscosimetric Index
1	Little's disease	7 yr.	Neg.	8	Neg.	1111000000	1.33500	1.05
2	Little's disease	3 yr.	Neg.	26	Neg.	0000000000	1.33487	1.05
3	Little's disease	17 mo.	Neg.	0	Neg.	.....	1.33472	1.09
4	Little's disease	12 mo.	Neg.	3	Neg.	0001100000	1.33529	1.06
5	Epilepsy	47 yr.	Neg.	2	Neg.	0011110000	1.33516	1.06
6	Epilepsy	11 yr.	.....	..	Neg.	0000000000	1.33498	1.11
7	Epilepsy	6 yr.	Neg.	4	Neg.	1222100000	1.33508	1.05
8	10/24/24 Epilepsy and idiocy	15 mo.	Neg.	12	Neg.	0111100000	1.33509	1.06
	11/ 4/24	.....	Neg.	..	Neg.	1110000000	1.33493	1.07
9	Epilepsy	3 yr.	Neg.	0	Neg.	0000000000	1.33517	1.07
10	Epilepsy	36 yr.	Neg.	3	Neg.	0222100000	1.33510	1.05
11	Jacksonian epilepsy	18 mo.	Neg.	10	Neg.	0111000000	1.33499	1.06
12	2/29/25 Epilepsy and cocain poisoning	19 yr.	Pos.	59	Neg.	1222100000	1.33511	1.05
	3/3/25	.....	Neg.	0	Neg.	.....	1.33508	1.05
13	Epilepsy and chronic nephritis	49 yr.	Neg.	8	Neg.	1223321000	1.33514	1.05
14	Epilepsy	21 yr.	Neg.	0	Neg.	1244320000	1.33514	1.05
15	Epilepsy	8 yr.	Neg.	4	Neg.	0000000000	1.33515	1.06
16	Mongolian idiocy	18 mo.	Neg.	6	Neg.	0012100000	1.33500	1.05
17	Imbecility	2 yr.	Neg.	0	Neg.	0000001100	1.33514	1.05
18	Encephalitis, active	45 yr.	Neg.	4	Neg.	0011221000	1.33511	1.04
19	Encephalitis, active	15 yr.	Neg.	4	Neg.	0111000000	1.33509	1.05
20	Encephalitis, recovered	13 yr.	Neg.	1	Neg.	0000000000	1.33527	1.05
21	Encephalitis, recovered	5 yr.	Neg.	8	Neg.	.....	1.33498	1.05
22	Encephalitis, recovered	9 yr.	Neg.	7	Pos.	0023320000	1.33502	1.05
23	Pneumonia and otitis media	2 yr.	Neg.	6	Neg.	0000000000	1.33520	1.05
24	Pneumonia	6 yr.	Neg.	2	Neg.	0133000000	1.33486	1.06
25	Pneumonia	11 yr.	Neg.	0	Neg.	.....	1.33497	1.08
26	Erysipelas	7 yr.	Neg.	0	Neg.	0000000000	1.33509	1.05
27	Otitis media	16 mo.	Neg.	4	Neg.	0000000000	1.33494	1.05
28	1/15/25 Otitis media and sinus thrombosis	12 yr.	Neg.	0	Neg.	0000000000	1.33506	1.06
	1/21/25 Otitis media and pericarditis	.....	Neg.	83	.....	.....	1.33478	1.05
	1/22/25	.....	Neg.	10	.....	.....	1.33509	1.05
29	Otitis media	2 yr.	Neg.	8	Neg.	0000000000	1.33481	1.05
30	Otitis media and acute nephritis	13 yr.	Neg.	0	Neg.	0011100000	1.33521	0.05
31	Sepsis	19 yr.	Neg.	0	Neg.	0002110000	1.33490	1.05
32	Hypertension and angiospasm	47 yr.	Neg.	8	Neg.	0012320000	1.33504	1.05
33	Hypertension and diabetes mellitus	52 yr.	Neg.	0	Neg.	0000000000	1.33522	1.05
34	Hypertension	50 yr.	Neg.	2	Neg.	0000000000	1.33513	1.05
35	Hypertension	34 yr.	Neg.	4	Neg.	0000000000	1.33500	1.05
36	Hypertension	48 yr.	Neg.	0	Neg.	0000000000	1.33502	1.10
37	Hypertension and cerebral thrombosis	60 yr.	Neg.	12	Neg.	0000000000	1.33509	1.05
38	Hypertension and cerebral hemorrhage	54 yr.	Neg.	7	Neg.	0000000000	1.33532	1.05
39	Hysteria	10 yr.	Neg.	4	Neg.	0000000000	1.33517	1.05
40	Senility	59 yr.	Neg.	9	Neg.	0012220000	1.33528	1.07
41	Hyperthyroidism	36 yr.	Neg.	0	Neg.	0011110000	1.33501	1.07
42	Chronic nephritis	19 yr.	Neg.	4	Neg.	.....	1.33510	1.05
43	Senility	37 yr.	Neg.	2	Neg.	0000000000	1.33519	1.04
44	Aortitis	65 yr.	Pos.	80	Neg.	0000000000	1.33508	1.06
45	Myocarditis	50 yr.	Pos.	14	Neg.	0033200000	1.33496	1.05
46	Ménière's disease	59 yr.	Neg.	2	Neg.	0000000000	1.33509	1.05
47	Rachitis	15 mo.	Neg.	6	Neg.	0000000000	1.33492	1.05
48	Infected tonsils	32 yr.	Neg.	0	Neg.	0111000000	1.33513	1.05
49	Appendicitis	26 yr.	Neg.	1	Neg.	0111100000	1.33500	1.05
50	Duodenal ulcer	50 yr.	Neg.	2	Neg.	0000000000	1.33517	1.05
51	Duodenal ulcer	38 yr.	Neg.	0	Neg.	0000000000	1.33514	1.05
52	Neurasthenia	20 yr.	Neg.	12	Neg.	0011100000	1.33509	1.05
53	Congenital heart disease	3 mo.	Neg.	4	Neg.	.....	1.33545	1.09
54	Occupational paresis	39 yr.	Neg.	0	Neg.	0000000000	1.33501	1.05
55	Multiple sclerosis	40 yr.	Neg.	0	Neg.	0012100000	1.33501	1.05
56	Brain tumor	3 mo.	Neg.	4	Neg.	.....	1.33523	1.05
57	Brain tumor	40 yr.	Neg.	12	Neg.	1111100000	1.33509	1.06
58	Spinal cord tumor	44 yr.	Pos.	120	Neg.	0011100000	1.33511	1.05
59	Compression myelitis and carcinoma of the breast	55 yr.	4+	6	Neg.	1110000000	1.33700	1.11
60	Hydrocephalus and encephalitis, recovered	13 mo.	Neg.	0	Neg.	0000000000	1.33518	1.09
61	Hypdocephalus and mongolian idiocy	12 mo.	Neg.	0	Neg.	0000000000	1.33511	1.05
62	Hydrocephalus, congenital	3 mo.	4+	..	.....	.....	1.33747	1.20

TABLE 3.—*Refractometric and Viscosimetric Readings in Syphilitic Fluid*

Case	Disease	Age	Globulin	Cells	Wassermann Reaction	Colloidal Gold Test	Refractometric Index	Viscosimetric Index
		A. Active						
1	Tabes dorsalis	32 yr.	4+	20	4+	0014420000	1.33524	1.04
2	Involvement of central nervous system	49 yr.	1+	222	4+	0244444431	1.33521	1.05
3	Involvement of central nervous system	28 yr.	4+	240	4+	0022332100	1.33529	1.06
		B. Inactive						
4	Neurovascular	27 yr.	2+	..	.....	.....	1.33535	1.07
5	Inactive	30 yr.	Neg.	0	Neg.	0012221000	1.33514	1.06
6	Inactive	37 yr.	Neg.	0	Neg.	0000000000	1.33513	1.05
7	Inactive	28 yr.	1+	12	Neg.	0000034300	1.33526	1.05
8	Central nervous system	18 yr.						
	(a) 1/16/25	.....	4+	40	Neg.	1123332100	1.33520	1.07
	(b) 1/17/25	.....	4+	27	.....	.....	1.33552	1.07
	(c) 1/25/25	.....	4+	25	.....	.....	1.33529	1.06
9	General paresis	48 yr.	4+	55	Neg.	1133333100	1.33524	1.05
10	Central nervous system	61 yr.	Neg.	0	Neg.	0012210000	1.33517	1.06
11	General paresis	62 yr.	Neg.	0	Neg.	0001110000	1.33557	1.06
12	Vascular, inactive	55 yr.	Neg.	9	Neg.	0012210000	1.33515	1.06
13	Inactive	44 yr.	Neg.	0	Neg.	0011100000	1.33513	1.05
14	Meningitic	11 yr.	Neg.	13	Neg.	0023321000	1.33513	1.05

TABLE 4.—*Refractometric and Viscosimetric Readings in Meningitic Fluid*

Case	Disease	Age	Globulin	Cells	Wassermann Reaction	Colloidal Gold Test	Refractometric Index	Viscosimetric Index
1	Tuberculous meningitis	7 yr.	.....	140	Neg.	0001333200	1.33490	1.05
2	Tuberculous meningitis	18 yr.	1+	165	Neg.	0000233100	1.33616	1.15
3	Tuberculous meningitis	43 yr.	1+	110	Neg.	.....	1.33570	1.18
4	Tuberculous meningitis	2 yr.	2+	194	Neg.	0011233210	1.33523	1.09
5	Tuberculous meningitis	5 mo.	4+	178	Neg.	0122344110	1.33552	1.06
6	Tuberculous meningitis	5 yr.	.....	90	Neg.	0002330000	1.33473	1.05
7	Tuberculous meningitis	18 mo.	.....	25	Neg.	.....	1.33487	1.06
8	Meningococcus meningitis	25 mo.						
	(a) 9/19/24 Before serum	.....	4+	10,000	Neg.	0001123443	1.33525	1.14
	(b) 9/20/24 After 20 c.c. of serum	.....	1+	.....	.....	.....	1.33540	1.13
	(c) 9/21/24 After 60 c.c. of serum	.....	1+	.....	.....	.....	1.33536	1.11
	(d) 9/21/24 After 80 c.c. of serum	.....	1+	.....	.....	.....	1.33555	1.10
	(e) 9/22/24 After 100 c.c. of serum	.....	1+	.....	.....	.....	1.33521	1.12
	(f) 9/23/24 After 120 c.c. of serum	.....	1+	.....	.....	.....	1.33574	1.11
	(g) 9/24/24 After 140 c.c. of serum	.....	1+	2,000	.....	.....	1.33644	1.12
	(h) 9/29/24 Improved	.....	.....	.....	.....	.....	1.33591	1.08
9	10/5/24 Meningococcus meningitis	5 mo.	4+	4,190	Neg.	0001123454	1.33543	1.14
	10/6/24 After 15 c.c. of serum (prognosis grave)	.....	4+	.....	.....	.....	1.33524	1.07
10	Meningococcus meningitis	.....	.....	4,900	.....	.....	.....	.....
	(a) 10/10/24 Before serum	.....	4+	.....	Neg.	0000255442	1.33571	1.13
	(b) 10/11/24 After 80 c.c. of serum	.....	4+	1,944	.....	.....	1.33510	1.10
	(c) 10/12/24 After 110 c.c. of serum	.....	4+	3,798	.....	.....	1.33500	1.10
	(d) 10/13/24 After 140 c.c. of serum	.....	4+	2,574	.....	.....	1.33487	1.10
	(e) 10/13/25 After 170 c.c. of serum, condition poor	.....	4+	3,024	.....	.....	1.33533	1.11
11	Streptococcus meningitis	9 yr.	Neg.	.....	Neg.	.....	1.33517	1.06
12	Streptococcus meningitis	4 yr.	.....	.....	Neg.	1111234444	1.33504	1.05
	(a) 1/6/25	.....	Neg.	7	Neg.	.....	.....	.....
	(b) 1/21/25	.....	Neg.	12	.....	.....	1.33497	1.05
	(c) 2/1/25	.....	.....	.....	Neg.	0000123433	1.33525	1.05
13	Streptococcus meningitis	55 yr.	4+	4,752	Neg.	0000034444	1.33593	1.08
14	Streptococcus meningitis (Postmortem fluid)	8 mo.	.....	.....	.....	.....	1.33924	1.31
15	Streptococcus meningitis	4 mo.						
	(a) 3/22/25 Ventricular fluid	.....	4+	100	.....	.....	1.33673	1.13
	(b) 3/23/25 Ventricular fluid	.....	4+	200	.....	.....	1.33703	1.14
	(c) 3/25/25 Ventricular fluid	.....	.....	.....	.....	.....	1.33704	1.13
16	Pneumococcus meningitis	18 mo.	4+	2,578	Neg.	0013333332	1.33639	1.09
17	Pneumococcus meningitis	2 mo.	4+	400	Neg.	0000144444	1.33518	1.08

Meningitic Fluid.—In seven cases of tuberculous meningitis, the reading ranged from 1.33473 to 1.33616, with an average reading of 1.33530. In fifteen fluids from three patients with meningococcus meningitis, the readings varied between 1.33487 and 1.33644, with an average reading of 1.33544, most fluids having a refractometric reading higher than the usual figures for nonmeningitic fluid. In eleven fluids from seven patients with other purulent meningitis, the reading varied between 1.33497 and 1.33924, with an average of 1.33618, most fluids having a high refractometric reading (Table 4).

The refractometric readings in the nonmeningitic and the nonsyphilitic cases, with the exception of one case of hydrocephalus and one case of compression myelitis, varied between 1.33472 and 1.33545. This differs only slightly from Molnar's figures, as in his series of "normal cases" the readings varied between 1.33486 and 1.33517. It also differs only very slightly from Polanyi's figure, which was 1.33554 at 20 degrees C. The high reading in our case of hydrocephalus agrees with the reading of Molnar, whose figures in one case of hydrocephalus was 1.3386, even higher than in our case. Our readings in cases of brain tumors do not justify the assumption of Molnar that the refractive index may be of diagnostic value in cases of brain tumor. In our three cases of brain and spinal cord tumors our readings were low.

VISCOSIMETRIC READINGS

In sixty-six nonmeningitic and nonsyphilitic fluids, the viscosimetric reading in sixty-two cases ranged between 1.04 and 1.09, with an average of 1.05. One case of hypertension, one of epilepsy and one of compression myelitis due to carcinoma gave a reading of 1.10 or over. The case of congenital hydrocephalus gave a reading of 1.20. In syphilitic fluids, both active and inactive, the viscosity varied between 1.04 and 1.07, with an average of 1.05. In the seven cases of tuberculous meningitis the viscosity varied between 1.05 and 1.18, with an average reading of 1.09. The fifteen determinations of fluids from cases of meningococcus meningitis ranged in their viscosimetric readings between 1.07 and 1.14, with an average reading of 1.11. It should be remembered, however, that some of the fluids in this group of cases were drawn after antimeningococcus serum had been given. The viscosity in other suppurative meningitides varied between 1.05 and 1.31, with an average of 1.11.

There is very little data in the literature on the viscosity of the cerebrospinal fluid. Polanyi found it to vary between 1.020 and 1.027

at 38 degrees C., using water as the standard of 1. In our previous work,[6] we found the viscosity between 1.0424 and 1.0489 compared to water. We used the Ostwald apparatus for our first series of determinations. In the present series, as stated above, we used the Hess instrument.

SUMMARY

1. Sixty-six specimens of cerebrospinal fluid obtained from nonmeningitic and nonsyphilitic patients gave a refractometric reading of 1.33472 to 1.33545, with an average of 1.33508. There were two exceptions to this rule, namely, one case of hydrocephalus and one case of compression myelitis, both of which gave an unusually high reading.

2. In fluid from active and inactive syphilis, the refractometric reading varied between 1.33513 and 1.33557, with an average of 1.33525.

3. Seven cases of tuberculous meningitis gave refractometric readings varying between 1.33475 and 1.33616, with an average of 1.33530. In fifteen fluids from three cases of meningococcus meningitis, the readings varied between 1.33487 and 1.33644, with an average reading of 1.33544. Eleven fluids from seven cases of other forms of purulent meningitis varied between 1.33497 and 1.33924, with an average reading of 1.33618.

4. The viscosity in sixty-two out of sixty-six fluids from nonmeningitic cases ranged between 1.04 and 1.09, with an average reading of 1.05. The viscosity in seven fluids from cases of tuberculous meningitis varied between 1.05 and 1.18, with an average reading of 1.09. The viscosity in fifteen fluids of meningococcus meningitis varied between 1.07 and 1.14, with an average of 1.11. The viscosity in fluids from other forms of suppurative meningitis also averaged 1.11.

5. The refractometer and viscosimeter may serve as a means of determining a marked increase in the protein of cerebrospinal fluid, but cannot be used for the determination of a slight increase in the protein.

6. A marked increase in the refractometric and viscosimetric readings speaks for a pathologic process of the nervous system, such as meningitis, obstructive hydrocephalus or compression myelitis. Normal refractometric and viscosimetric readings do not exclude a pathologic process of the nervous system.

7. Refractometric and viscosimetric readings do not change with the age of the fluid.

8. The cerebrospinal fluid must be free from blood for refractometric and viscosimetric determinations.

---

6. Levinson, A.: Cerebrospinal Fluid in Health and in Disease, Ed. 2, St. Louis, C. V. Mosby Company, 1923.

Book Reviews

DISEASES OF THE BRONCHI, LUNGS AND PLEURA. By FREDERICK T. LORD, M.D., Visiting Physician, Massachusetts General Hospital; Instructor in Medicine, Harvard Medical School. Second Edition, Thoroughly Revised, with the Addition of Chapter on Pulmonary Tuberculosis. Pp. 776, with 110 illustrations. Price, $8.00. Philadelphia: Lea & Febiger, 1925.

The first edition of Lord's book on diseases of the bronchi, lungs and pleura, which appeared in 1915, was favorably received by the profession. Many expressed regret that a consideration of tuberculosis was omitted. In the present edition more than 100 pages are devoted to a comprehensive discussion of the subject. In addition to this valuable feature, the book has been revised and considerable new material has been added. Among the most important additions are those concerning atelectasis, the etiology and treatment of bronchial asthma, the newer conceptions of the resolution and recovery from lobar pneumonia, streptococcus bronchopneumonia and empyema, bronchoscopy, increase in the scope of thoracic surgery, the roentgen ray in diagnosis and the treatment of acute empyema by closed drainage.

In this edition the same high standards are maintained and the profession is given the benefit of fifteen years' additional experience by one who has made an extensive study of the field. The book will therefore serve as a valuable reference for the student and teacher and a trustworthy guide for the practitioner.

TRAITEMENT DU DIABETE. By PEDRO ESCUDERO, Professeur de clinique medicale l l'Universite de Buenos Ayres. Paris: Norbert Maloine, 1925.

A reviewer, pondering over modern thought and modern publications on diabetes, encounters difficulty in harmonizing the many divergent views of practice. High fats and low fats are advocated, protein is used and abused, the safe fatty acid-glucose ratio is variously estimated, and one wonders over the fact that most patients who are adequately treated get along equally well under so many different regimens. The reason must be, of course, that each system has certain fundamental similarities in principle, even though the existing confusion hides the parallelism.

To such a reviewer this book from a South American colleague comes as a real pleasure. The basis of diabetic treatment has always been the same—the dietetic regimen. Insulin has not modified or simplified this treatment, but has rendered it really efficacious. No extreme ideas of dietotherapy are accepted; the perversion of metabolism is not systematic; each diabetic patient must have his own regimen. "Hyponutrition" (undernourishment) is used in the beginning of treatment, and starvation as a heroic method in the control of acidosis. But to establish "le régime definitif," preconceived preference does not prevent the employment of protein, fat and carbohydrates entirely as dictated by the needs and capacity of the individual patient. Patients with severe diabetes require insulin. The physician wastes his time on patients who will not, or cannot, cooperate.

These few paraphrases from the preface indicate the character of the book. Clinical details are many, discussion of various schemes of treatment full. Excellent food tables and diet lists are found at the end; insulin is thoroughly and practically discussed in an appendix of thirty-two pages. We believe that this volume is not surpassed by any French book on the subject.

MEDICINE: AN HISTORICAL OUTLINE. By M. G. SEELIG, M.D., Professor of Clinical Surgery in the Washington University School of Medicine, Baltimore. Baltimore: Williams & Wilkins Co., 1925.

In a delightful foreword, Dr. Fielding H. Garrison speaks of the device of lecturing as a dubious one in any subject, but adds with truth that the lectures under review are "fresh, informing, brief and to the point." Dr. Seelig has done a useful piece of work in preparing an outline of medical history, which no doubt was followed with enthusiasm by his hearers. It is fortunate that the lectures have appeared in book form and can be read in a few hours and referred to at will.

Dr. Seelig's book is an outline, but it also is a sound guide to the beginner in medical study or to the intelligent layman who wishes to gain a rapid view of the subject. The informed, even the specialist in medical history, can read it with pleasure and profit, if only to get the author's method and point of view.

The work begins with the evidences of superstition and folklore in medicine, with pithy comments on many details, and early discloses a broad and accurate knowledge of general history. Egyptian, Babylonian and Jewish medicine are adequately touched on. Greek and Roman medicine are described in a few pages. After brief consideration of the Middle Ages, the narrative becomes more detailed and follows through the centuries. This division of time is convenient and will be found, especially by the beginner, to have distinct advantages.

It is easy to criticize details in any work so condensed as this, but there is nothing serious to comment on here. Dr. Seelig is in good company in his treatment of Paracelsus, yet the skeptic may think that he has overidealized that strange character. Perhaps the account of Paré will be more generally acceptable; many will think that John Hunter has been dismissed too soon. A few questionable or inaccurate statements may be ascribed to hasty preparation. It seems erroneous to speak of the popularization of the clinical thermometer in the eighteenth century. Parry's description of exophthalmic goiter in 1786 exerted no influence until many years later. Some chronologic dislocations occur, as the consideration of Bichat before Morgagni. The proofreading could have been improved. The faults, however, are trifling in comparison with the general accuracy, the fulness, and the terse and engaging style of the author. It is to be hoped that the volume will have wide use among students in premedical and medical years. Public libraries cannot do without it.